2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of cyanide. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure-inhalation, oral, and dermal; and then by health effect-death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods-acute (14 days or less), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health

effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for cyanide. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

This section provides information regarding known health effects of cyanide exposure. Exposure to hydrogen cyanide (HCN) gas is most common by inhalation. In the discussion below, inhalation exposures are expressed as ppm hydrogen cyanide. Exposure to cyanide can also occur by inhalation of cyanogen gas, a dimer of cyanide. However, cyanogen breaks down in aqueous solution into cyanide ion (CN^{-1}) and OCN^- ions (Cotton and Wilkinson 1980). The rate of the breakdown depends on pH and is faster in basic media (e.g., hydrogen cyanide is in equilibrium as H^+ and CN^- in blood with a pH of

7.38-7.44) than in acidic media (e.g., hydrogen cyanide is the only species in stomach contents at a pH of 3). The amount of cyanide ion formed within a body tissue or fluid as a result of exposure to cyanogen has been reported; however, the amount varies with type of body tissue and fluid. Thus, it is difficult to estimate cyanide levels in body tissues after cyanogen exposure. Therefore, studies regarding exposure to cyanogen are discussed in the text as ppm cyanogen, but are not included in Levels of Significant Exposure tables or figures.

Oral exposure to cyanide usually results from accidental, homicidal, or suicidal ingestion of cyanide salts. Sodium cyanide and potassium cyanide are the most frequently studied cyanide compounds. Copper cyanide, potassium silver cyanide, silver cyanide, and calcium cyanide are other compounds that humans could encounter through oral or dermal exposure. Cassava roots and certain fruit pits contain compounds that can be broken down to form cyanide. Cassava roots form the staple diet of some populations in Africa, Central and South America, and Asia. However, it must be noted that cassava roots are notoriously deficient in protein and other nutrients and contain many other compounds, in addition to cyanide, that could be responsible for some of the observed toxic effects. Thiocyanate is a metabolite of cyanide that is formed in the body after exposure to cyanide compounds. When possible, all oral exposures are expressed as mg CN^-/kg/day.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

2.2.1 Inhalation Exposure

2.2.1.1 Death

Inhalation of sufficient concentrations of hydrogen cyanide gas can rapidly cause death, which has led to the use of hydrogen cyanide in gas chamber executions (Wexler et al. 1947). An average fatal concentration for humans was estimated as 546 ppm hydrogen cyanide (524 ppm cyanide) after a lo-minute exposure (McNamara 1976, as cited in Ballantyne 1987). In one case, a worker exposed to 200 ppm hydrogen cyanide (192 ppm cyanide) in a silver plating tank became unconscious and eventually died even though he had received antidotal therapy in a hospital (Singh et al. 1989). In other cases, exposure to 270 ppm hydrogen cyanide (259 ppm cyanide) led immediately to death, 18 1 ppm hydrogen cyanide exposure (174 ppm cyanide) was fatal after 10 minutes, and 135 ppm hydrogen cyanide (130 ppm cyanide) after 30 minutes in humans (Dudley et al. 1942).

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Levels of acute exposure resulting in animal deaths were reported in numerous studies and LC_{50} (lethal concentration, 50% death) values were provided for several species. Inhalation LC_{50}values of hydrogen cyanide in rats ranged from 143 ppm (137 ppm cyanide) for 60 minutes to 3,417 ppm (3,280 ppm cyanide) for 10 seconds (Ballantyne 1983a). Exposure to cyanide resulted in similar LC_{50} values in mice (Higgins et al. 1972; Matijak-Schaper and Alarie 1982). LC_{50} values for hydrogen cyanide in rabbits ranged from 188 ppm (18 1 ppm cyanide) for 30 minutes to 2,200 ppm (2,112 ppm cyanide) for 45 seconds (Ballantyne 1983a). Lethal concentrations were also reported in experiments with dogs exposed for acute (Haymaker et al. 1952) and intermediate durations (Valade 1952). Both studies used a small number of dogs for different exposure regimens so that statistical significance could not be evaluated.

The LC_{50} values in each species and LOAEL values for death in humans in the acute-, and intermediate duration category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The systemic effects observed in humans and animals after inhalation exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

Respiratory Effects. Initially, respiration is stimulated, but later dyspnea occurs in patients admitted to a hospital after acute hydrogen cyanide exposure (Chen and Rose 1952; Peden et al. 1986; Potter 1950). The levels of exposure in these accidental poisonings were not provided. Nasal irritation was reported in volunteers exposed to 16 ppm cyanogen (8 ppm cyanide) for 6-8 minutes (McNerney and Schrenk 1960). No effects were reported at 8 ppm cyanogen (4 ppm cyanide).

Dyspnea was observed in workers chronically exposed (5-15 years) to 6.4-10.4 ppm of an unspecified cyanide form evolved from sodium cyanide and copper cyanide during electroplating (El Ghawabi et al. 1975) and in workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) in a silver-reclaiming facility (Blanc et al. 1985). Other complaints included cough, sore throat, altered sense of smell, nasal congestion, epistaxis, and hemoptysis. However, exposure to other chemicals such as cleaners and cutting oils also occurs in electroplating operations.

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Human	10 min				524 (LC_{50})	McNamara 1976 HCN
2	Human	NS				192 M (fatal after 3 days)	Singh et al. 1989 HCN
3	Rat (NS)	60 min				137 (LC_{50} in 60 min)	Ballantyne 1983a HCN
4	Rat (Wistar)	5 min				483 (LC_{50})	Higgins et al. 1972 HCN
5	Mouse (ICR)	5 min				310 (LC_{50})	Higgins et al. 1972 HCN
6	Mouse (ICR)	3 min				400 M (90% lethality)	Hume et al. 1995 HCN
7	Mouse (Swiss-Webster)	30 min				159 M (LC_{50})	Matijak-Schaper and Alarie 1982 HCN
8	Rabbit (NS)	35 min				181 (LC_{50} in 35 min)	Ballantyne 1983a HCN
Systemic							
9	Human	13 min	Ocular		434 M (slight loss of peripheral vision after recovery)		Bonsall 1984 HCN
10	Monkey (Cyno-molgus)	30 min	Resp			96 (severe dyspnea)	Purser et al. 1984 HCN
			Cardio			96 (bradycardia, arrhythmia, T-wave abnormalities)	

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
11	Mouse (Swiss-Webster)	30 min	Resp			60 M (DC_{50})	Matijak-Schaper and Alarie 1982 HCN
	Neurological						
12	Human	13 min				434 M (coma)	Bonsall 1984 HCN
13	Monkey (Cyno-molgus)	30 min				96 (semiconsciousness, disrupted respiration, EEG changes)	Purser et al. 1984 HCN
	INTERMEDIATE EXPOSURE						
	Death						
14	Dog (NS)	28 d 2-day intervals 30 *min*/d				43 (1/4 died)	Valade 1952 HCN
	Systemic						
15	Rat (Long- Evans)	5 x/20 d 4 d intervals 12.5 min/x	Cardio			192 M (increased creatine phosphokinase activity)	O'Flaherty and Thomas 1982 HCN
16	Dog (NS)	28 d 2-day intervals 30 min/d	Resp			43 (dyspnea)	Valade 1952 HCN
			Gastro		43 (vomiting, tenesmus, and diarrhea)		

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
Neurological							
17	Dog (NS)	28 d 2-day intervals 30 min/d				43 (tremors, stiffness, ataxia, vasodilation and hemmorhage, atrophy of Purkinje and glial cells)	Valade 1952 HCN
CHRONIC EXPOSURE							
Systemic							
18	Human	NS	Resp		14M (dyspnea)		Blanc et al. 1985 HCN
			Cardio		14M (palpitations, chest pain)		
			Gastro		14M (nausea)		
			Endocr		14M (increased mean thyroid stimulating hormone levels)		
			Dermal		14M (rash)		
			Ocular		14M (eye irritation)		
			Bd Wt		14M (approximately 8% weight loss)		

Table 2-1. Levels of Significant Exposure to Cyanide - Inhalation (continued)

Key to[a] figure	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
19	Human	5-15 yr (occup)	Resp		6.4 M (dyspnea, irritation of throat)		El Ghawabi et al. 1975 NaCN
			Cardio		6.4 M (precordial pain)		
			Gastro		6.4 M (vomiting)		
			Hemato		6.4 M (increased hemoglobin and lymphocytes)		
			Endocr		6.4 M (thyroid enlargement)		
			Dermal	10.4 M			
			Ocular		6.4 M (lacrimation)		
	Neurological						
20	Human	NS				14 M (persistent headache, dizziness, paresthesia)	Blanc et al. 1985 HCN
21	Human	5-15 yr (occup)				6.4 M (confusion, hallucination, headache, dizziness, weakness)	El Ghawabi et al. 1975 NaCN

[a]The number corresponds to entries on Figure 2-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); DC_{50} = concentration that resulted in 50% decrease in average respiratory rate; EEG = electroencephalogram; Endocr = endocrine; F = female; Gastro = gastrointestinal; HCN = hydrogen cyanide; Hemato = hematological; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minutes; NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; (occup) = occupational; Resp = respiratory; sec = second(s); yr = year(s); x = time(s)

Figure 2-1. Levels of Significant Exposure to Cyanide - Inhalation

Acute (≤14 days)

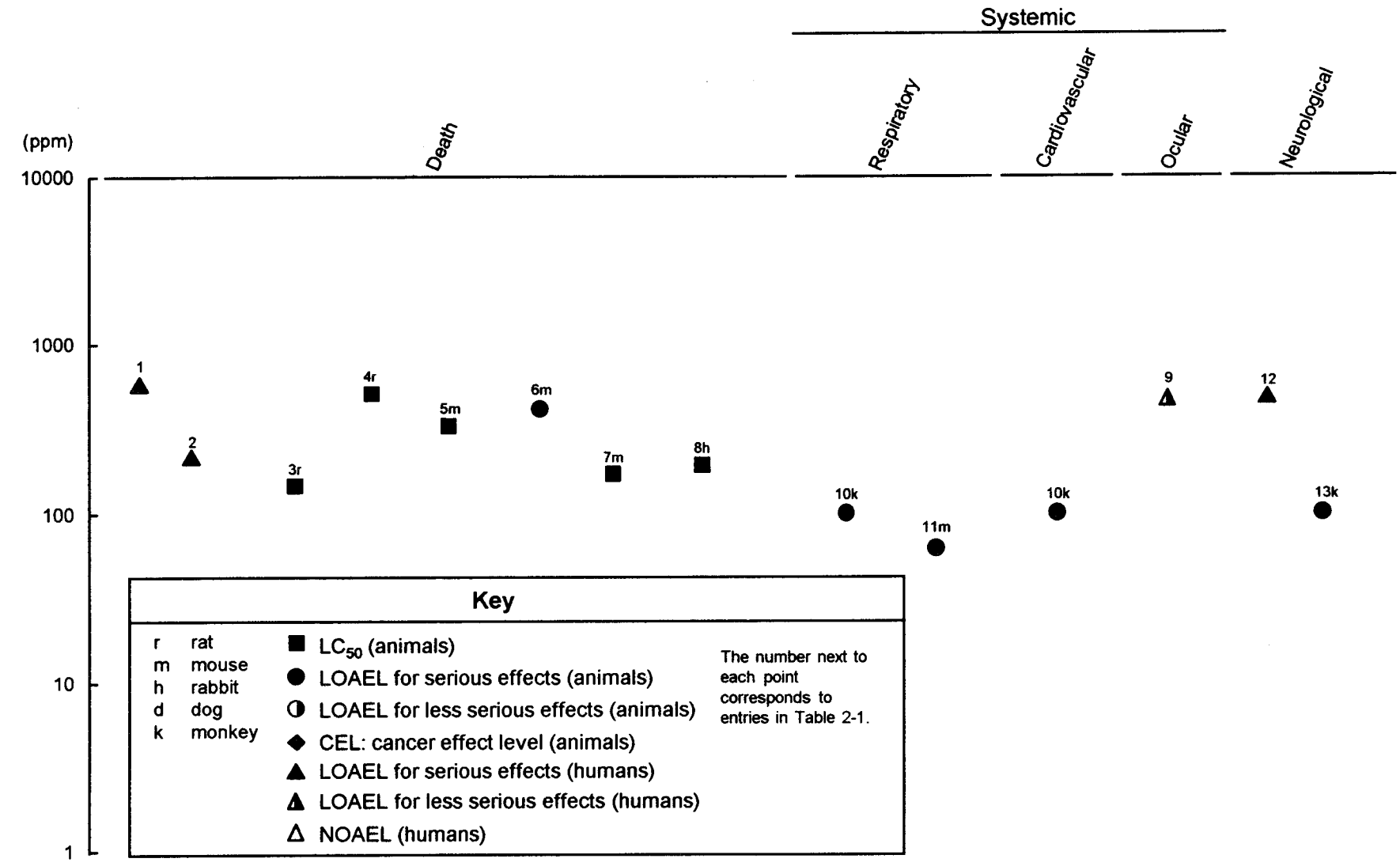


Figure 2-1. Levels of Significant Exposure to Cyanide - Inhalation (cont.)

Intermediate (15-364 days)

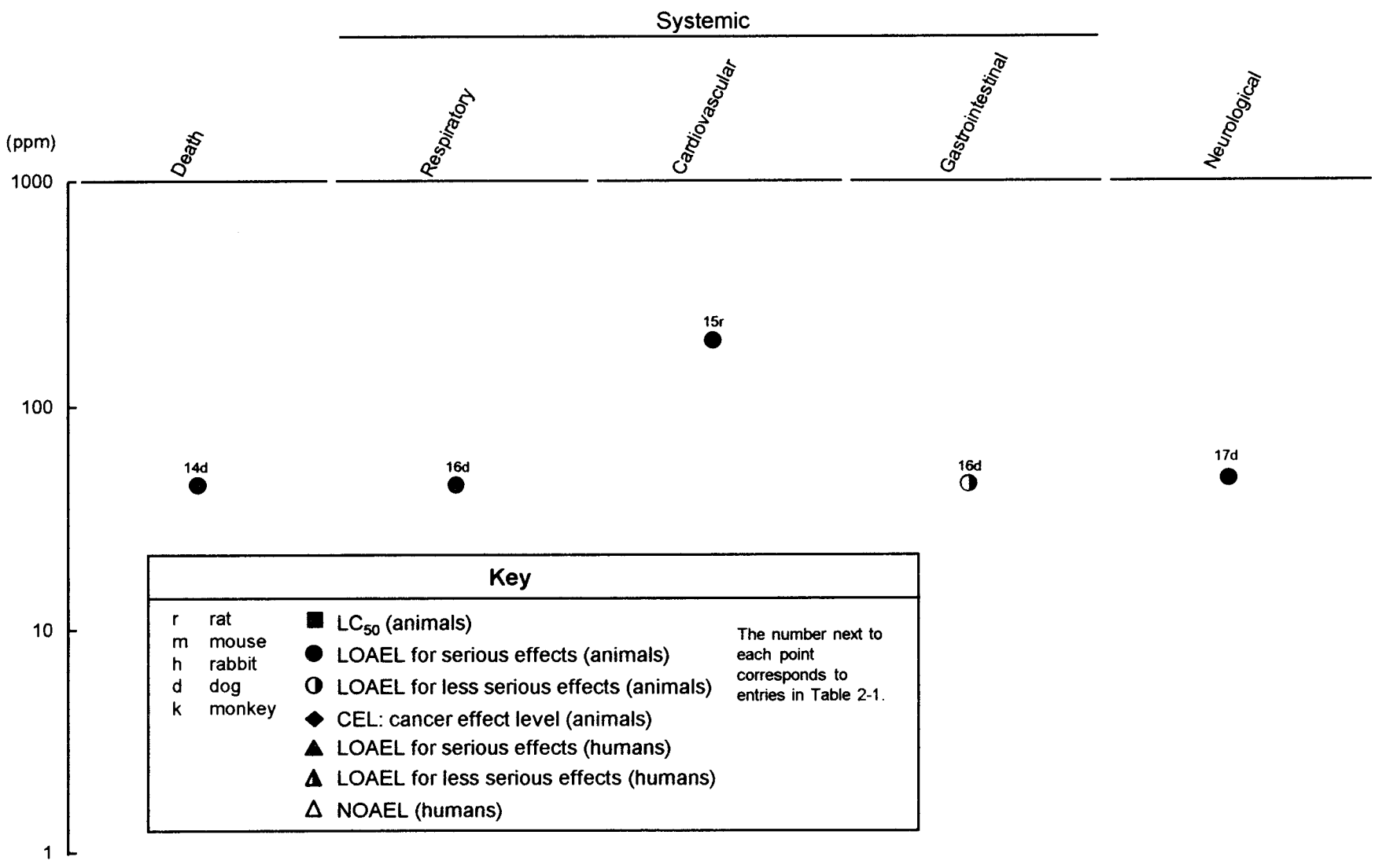
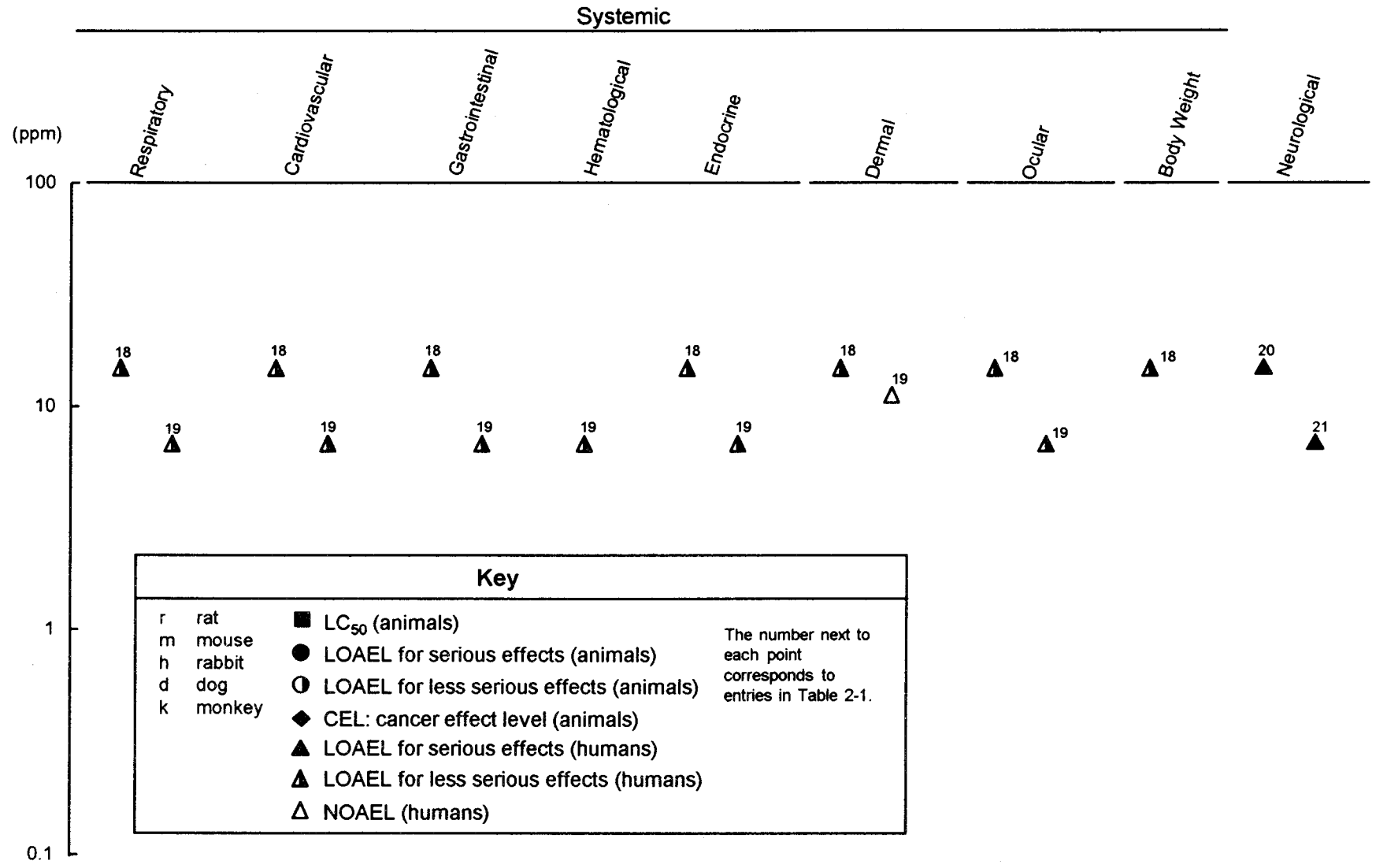


Figure 2-1. Levels of Significant Exposure to Cyanide - Inhalation (cont.)

Chronic (≥365 days)



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Asphyxia has been observed in rats exposed to 250 ppm cyanogen (125 ppm cyanide) for 7.5-120 minutes (McNemey and Schrenk 1960), asphyxia and pulmonary edema were observed in dogs exposed to concentrations ranging from 149 to 633 ppm hydrogen cyanide (143-608 ppm cyanide) for 2-10 minutes (Haymaker et al. 1952), while severe dyspnea was observed in monkeys exposed to 100 ppm hydrogen cyanide (96 ppm cyanide) for 30 minutes (Purser et al. 1984). Exposure to 63 ppm hydrogen cyanide (60 ppm cyanide) for 30 minutes resulted in a 50% decrease in respiratory rate of mice due to depression of the respiratory center (Matijak-Schaper and Alarie 1982).

In intermediate-duration studies, no respiratory effects were reported in rats exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months, and a decrease in total lung moisture content was the only finding in monkeys exposed to 11 ppm cyanogen (22 ppm cyanide), also for 6 months (Lewis et al. 1984). Dyspnea was found in dogs exposed to 45 ppm hydrogen cyanide (43 ppm cyanide) for 30 minutes a day at 2-8-day intervals for 28-96 days (Valade 1952).

Cardiovascular Effects. Wexler (1947) reported on four men executed by inhalation of hydrogen cyanide gas (concentration not reported). He reported a distinct slowing of the heart rate within l-3 minutes of exposure, with further changes in the heart rate, sinus irregularities, and audio-visual dissociation. Palpitations and hypotension were the most frequently reported cardiovascular effects in patients after accidental inhalation poisoning with cyanide; however, exact exposure levels were not known (Peden et al. 1986). Workers occupationally exposed to 6.4-10.4 ppm cyanide for 5-15 years, which evolved from sodium cyanide and copper cyanide during electroplating, complained of precordial pain (El Ghawabi et al. 1975). About 14% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) in a silver-reclaiming facility reported palpitations and 3 1% reported chest pain (Blanc et al. 1985). Exposure to other chemicals such as cleaners and cutting oils may have also occurred during electroplating operations.

Bradycardia, arrhythmias, and T-wave abnormalities were observed in monkeys exposed to 100 ppm hydrogen cyanide (96 ppm cyanide) for 30 minutes (Purser et al. 1984). Increased cardiac-specific creatinine phosphokinase activity was measured in blood samples from rats 2 hours after 12.5 minutes of exposure to 200 ppm hydrogen cyanide (192 ppm cyanide) for 20 days at 4-day intervals (O'Flaherty and Thomas 1982). However, no treatment-related changes were found in the hearts at histopathology. In addition, no cardiovascular effects were reported at necropsy in rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months (Lewis et al. 1984).

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Gastrointestinal Effects. Nausea or vomiting was reported in 69% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) in a silver reclaiming facility (Blanc et al. 1985). Vomiting was also reported in workers exposed to 6.4-10.4 ppm cyanide evolved from sodium cyanide and copper cyanide during electroplating (El Ghawabi et al. 1975), but exposure to other chemicals such as cleaners and cutting oils may have also contributed to the effects. The gastrointestinal effects resulting from cyanide exposure are probably provoked by central nervous system effects and/or by irritation of the gastric mucosa in cases in which the gas is swallowed during breathing.

Information regarding gastrointestinal effects in animals is limited to a report of vomiting in dogs exposed to 45 ppm hydrogen cyanide (43 ppm cyanide) for 28-96 days (Valade 1952).

Hematological Effects. Increased hemoglobin and lymphocyte count were observed in workers exposed to 6.4-10.4 ppm of an unspecified cyanide form during electroplating (El Ghawabi et al. 1975). The results were significantly different from controls. Furthermore, punctate basophilia of erythrocytes, which indicated toxic poisoning, was present in 28 of 36 subjects. However, exposure to copper, a known hematotoxic agent, also occurred during the electroplating operations. In another study (Kumar et al. 1992), an increase in neutrophil values, an increase in erythrocyte sedimentation rate, and a decrease in hemoglobin levels were noted in male workers exposed to unspecified concentrations of cyanide for an unspecified duration during case hardening and electroplating.

In animals, no hematological effects were found in rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) 6 hours per day, 5 days per week, for 6 months (Lewis et al. 1984).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to cyanide.

No musculoskeletal effects were observed in rats or monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 hours per day, 5 days per week for 6 months (Lewis et al. 1984).

Hepatic Effects. An increase in serum alkaline phosphatase was noted in workers exposed to unspecified levels of cyanide; however, serum bilirubin was found to be within the normal range in these workers (Kumar et al. 1992).

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Only one study reported on pathological and histopathological examinations of the liver in animals. No changes were found in rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months (Lewis et al. 1984).

Renal Effects. One study was located regarding renal effects in humans after inhalation exposure to cyanide. Singh et al. (1989) reported anuria followed by polyuria in a man who was occupationally exposed to 200 ppm hydrogen cyanide (192 ppm cyanide) for an unspecified length of time.
No histopathological changes were observed in kidneys of rats and monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) 6 hours per day, 5 days per week for 6 months (Lewis et al. 1984).

Endocrine Effects. Mean thyroid stimulating hormone (TSH) levels (all exposed workers) were significantly higher (although within normal limits) in workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) for an unspecified duration in a silver-reclaiming facility than in unexposed individuals ($P< 0.05$). T_3 levels in high exposure workers were also elevated relative to unexposed workers ($p<0.01$). Data for T_4 were not presented, but the investigators indicated that the absence of T_4 abnormalities could be accounted for by the time lapse between exposure and examination (median 10.5 months) (Blanc et al. 1985). Similarly, thyroid enlargement was present in 20 of 36 workers exposed, for 5-15 years, to 6.4-10.4 ppm cyanide evolved from sodium cyanide and copper cyanide. The endocrine effect may be due to formation of thiocyanate, a metabolite of cyanide. However, exposure to other chemicals such as cleaners and cutting oils also occurs during electroplating operations. Thyroid ^{131}I uptake was significantly higher when compared with the control group. This may be due to cyanide's ability to block iodine uptake and organification by the thyroid gland. Since the workers were away from work on the 2 days preceding the test, the results may be explained on the basis of acute cyanide withdrawal, as with other anti-thyroid agents, where sudden cessation of the drug leads to rapid accumulation of iodine in the iodine-depleted gland (El Ghawabi et al. 1975).

No studies were located regarding endocrine effects in animals after inhalation exposure to cyanide.

Dermal Effects. Cyanide caused a rash in 42% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) (Blanc et al. 1985). Brick-red chemical bums on the skin were observed in a man who was occupationally exposed to 200 ppm hydrogen cyanide (192 ppm cyanide) for an unspecified length of time (Singh et al. 1989). No dermatitis was reported in workers exposed to 6.4-10.4 ppm cyanide evolved from sodium cyanide and copper cyanide (El Ghawabi et al. 1975).

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No studies were located regarding dermal effects in animals after inhalation exposure to cyanide.

Ocular Effects. Cyanogen caused eye irritation in volunteers during acute exposure to 16 ppm (8 ppm cyanide) (McNemey and Schrenk 1960). No effect was observed in those exposed to 8 ppm cyanogen (4 ppm cyanide). Slight loss of peripheral vision was the only persistent finding from a case report of a man who had been exposed to 452 ppm hydrogen cyanide (434 ppm cyanide) for 13 minutes while cleaning a chemical tank (Bonsall 1984). During chronic occupational exposure, eye irritation occurred in workers of two electroplating factories (exposure levels not specified) (Chandra et al. 1988). In other studies, cyanide caused eye irritation in 58% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) (Blanc et al. 1985), and lacrimation in workers exposed to 6.4 ppm cyanide (El Ghawabi et al. 1975). The eye irritation may not be due solely to cyanide exposure, as electroplating workers may be exposed to a variety of chemicals that are irritating to the eyes.

Information regarding ocular effects in animals after inhalation exposure to cyanide is limited to a report of eye irritation in rats acutely exposed (7.5-120 minutes) to 250 ppm cyanogen (500 ppm cyanide) (McNemey and Schrenk 1960).

Body Weight Effects. In an occupational setting, loss of appetite was reported in 58% and weight loss (approximately 8%) in 50% of workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) for an unspecified duration in a silver-reclaiming facility (Blanc et al. 1985).

Decreased body weight was reported in rats exposed to 25 ppm cyanogen (50 ppm cyanide) 6 hours a day, 5 days a week for 6 months (Lewis et al. 1984).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to cyanide.

2.2.1.4 Neurological Effects

The central nervous system is a primary target for cyanide toxicity. Acute exposure of humans to fatal levels of hydrogen cyanide causes a brief stage of central nervous system stimulation followed by depression, convulsions, coma with abolished deep reflexes and dilated pupils, paralysis, and in some

cases, death (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989). Though clinical symptoms of cyanide poisoning are well recognized, specific dose-response data are generally not known. Acute exposure to lower concentrations can cause lightheadedness, breathlessness, dizziness, numbness, and headaches (Peden et al. 1986).

Chronic exposure of humans to potassium cyanide and other chemicals may have produced severe neurological effects such as hemiparesis and hemianopia (Sandberg 1967). During chronic occupational exposure, workers exposed to 15 ppm hydrogen cyanide (14 ppm cyanide) for an unspecified duration reported fatigue, dizziness, headaches, disturbed sleep, ringing in ears, paresthesias of extremities, and syncopes (Blanc et al. 1985). A dose-effect was demonstrated on high- and low-exposure jobs; however, exact cyanide concentrations in the air were not known. Neurological effects persisted in some workers even after a 10-month nonexposure period. Similar effects were observed in workers exposed to 6.4 ppm cyanide (El Ghawabi et al. 1975). Clinical symptoms included headaches, weakness, changes in taste and smell, dizziness, disturbances of accommodation, and psychosis. A recent study (Kumar et al. 1992) reported loss of delayed and immediate memory, and a decrease in visual ability, psychomotor ability, and visual learning in workers exposed to unspecified levels of hydrogen cyanide for an unspecified duration. In another study, chronic occupational exposure of workers (5-19 years) to hydrogen cyanide (exposure levels not specified) resulted in headaches and dizziness in workers (Chandra et al. 1988). Furthermore, when behavioral functions were tested in this cohort, an alteration of delayed memory and/or visual impairment was found in 31.5% of workers. However, exposure to other chemicals, such as cleaners and cutting oils, also occurs during electroplating operations.

The central nervous system is also a primary target for cyanide toxicity in animals. Following acute exposure, neurological effects before death included restless and panic movements, poor coordination, tremor, and lethargy in rats exposed to 250 ppm cyanogen (500 ppm cyanide) for 1.5-120 minutes (McNemey and Schrenk 1960). When rats were exposed to unspecified concentrations of hydrogen cyanide and kept unconscious for 20-60 minutes, lesions of various degrees developed in the brain (Hirano et al. 1967; Levine 1969; Levine and Stypulkowski 1959a). Necrosis was found mainly in the mid-sagittal sections of the brain. Demyelination was also reported and morphological signs indicative of remyelination were reported in rats several months after cyanide intoxication (Hirano et al. 1968), but it was apparent that this process was slow and incomplete. Acute exposure of dogs for 2-10 minutes, each to a different concentration ranging from 149 to 633 ppm hydrogen cyanide (143-608 ppm cyanide), resulted in motor incoordination, muscular rigidity, and coma (Haymaker et al. 1952). Extensive necrosis in the grey matter of the neural system was observed at necropsy. Acute exposure (30 minutes) to

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100 ppm hydrogen cyanide (96 ppm cyanide) induced semiconsciousness rapidly in monkeys (Purser et al. 1984). An increase in delta activity was observed in the electroencephalogram. Cyanide exposure levels in most acute duration studies were relatively high and usually caused death in some animals. OnIy transitory behavioral changes were reported in monkeys exposed to 25 ppm cyanogen (50 ppm cyanide) for 6 months (Lewis et al. 1984). No effects were found at 11 ppm cyanogen (22 ppm cyanide) exposure. Exposure of dogs to 45 ppm hydrogen cyanide (43 ppm cyanide) for 28-96 days caused tremors, convulsions, and coma (Valade 1952). Vascular and cellular lesions were found in the central nervous system.

The highest NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2- 1.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to cyanide:

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer effects in humans or animals after inhalation exposure to cyanide.

2.2.2 Oral Exposure

2.2.2.1 Death

An average fatal dose of 1.52 mg/kg cyanide for humans has been calculated from case report studies of intentional or accidental poisonings (EPA 1987a). The lowest fatal oral dose reported in humans is 0.56 mg/kg cyanide (Gettler and Baine 1938).

Oral LD_{50} (lethal dose, 50% death) values were calculated for rats as 3 mg CN^-/kg (Ballantyne 1988) or 8 mg CN^-/kg (Smyth et al. 1969) given as sodium cyanide. An LD_{50} of 2.7 mg CN^-/kg/day was reported for starved rats (Ballantyne 1988). However, since starvation rendered these animals physiologically compromised, this value should not be considered reliable. An acute LD_{50} of 22 mg CN^-/kg as calcium cyanide was reported in rats (Smyth et al. 1969). Acute LD_{50} values in rabbits showed little variation (2.34–2.7 mg CN^-/kg/day) regardless of whether the source was hydrocyanic acid, sodium cyanide, or potassium cyanide (Ballantyne 1983a). High mortality occurred in rats and mice that received a single dose of 4 and 6 mg CN^-/kg, respectively, in the form of potassium cyanide (Ferguson 1962). Greater dilution of dosages in water resulted in higher mortality. Increased mortality was observed in rats exposed to 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1987a) and to 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). Hemolytic anemia, which probably resulted from copper toxicity, caused death in rats exposed to copper cyanide (Gerhart 1987a). No deaths were reported in male and female rats exposed to 0.2–12.5 mg CN^-/kg/day in the drinking water for 13 weeks (NTP 1993).

When comparing the available acute lethal toxicity information for cyanide compounds, it was concluded that, for oral exposure, the molar lethal toxicities of hydrogen cyanide, sodium cyanide, and potassium cyanide are similar. Rabbits appeared to be more susceptible to the lethal toxicity of these three compounds than rats (Ballantyne 1988).

The LD_{50} and minimum lethal dose (LD_{LO}) values in each species and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Table 2-2. Levels of Significant Exposure to Cyanide - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
	ACUTE EXPOSURE							
	Death							
1	Rat (Sprague-Dawley)	once (GW)					4 (19/20 died)	Ferguson 1962 KCN
2	Rat (NS)	once (GW)					8 (LD_{50})	Smyth et al. 1969 NaCN
3	Rat (NS)	once (GW)					22 (LD_{50})	Smyth et al. 1969 Ca(CN)2
4	Mouse (Swiss-Webster)	once (GW)					6 (19/20 died)	Ferguson 1962 KCN
	Systemic							
5	Human	once (IN)	Resp				15 M (hyperventilation)	Liebowitz and Schwartz 1948 KCN
			Cardio				15 M (shallow pulse, inaudible heart sounds, enlarged heart)	
			Gastro		15M	(vomiting and nausea)		
			Hemato	15M				
			Musc/skel		15M	(generalized muscular rigidity)		
			Renal				15 M (albuminuria)	

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Neurological						
6	Human	once (IN)				15 M (coma)	Liebowitz and Schwartz 1948 KCN
	Reproductive						
7	Hamster (Syrian)	Gd 3-14 (F)		10.4 F			Frakes et al. 1986 Cassava
	Developmental						
8	Hamster (Syrian)	Gd 3-14 (F)				1.0 (23% decreased fetal weight and delayed ossification)	Frakes et al. 1986 Cassava
	INTERMEDIATE EXPOSURE						
	Death						
9	Rat (Sprague-Dawley)	90 d 1 x/d (G)				14.5 (23/40)	Gerhart 1987a CuCN
10	Rat (Sprague-Dawley)	90 d 1 x/d (G)				2.6 (9/40 died)	Gerhart 1987b KAg(CN)2

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
11	Rat (Sprague-Dawley)	90 d 1 x/d (G)	Resp	1.45	4.35 (labored respiration, severity not reported)		Gerhart 1987a CuCN
			Dermal		14.5 (discolored inguinal fur)		
			Ocular	14.5			
			Bd Wt	1.45 M	4.35 M (12% decreased body weight gain)		
12	Rat (Sprague-Dawley)	90 d 1 x/d (G)	Resp		0.8 (labored respiration, severity not reported)		Gerhart 1987b KAg(CN)2
			Cardio	7.8			
			Gastro	7.8			
			Hemato	2.6	7.8 (increased hemoglobin)		
			Hepatic	7.8			
			Renal	2.6	7.8 (increased BUN)		
			Dermal	0.8	2.6 (discolored fur)		
			Ocular	0.8		2.6 (corneal opacity)	
			Bd Wt	0.8 M		2.6 M (21% decreased body weight gain)	
13	Rat (Fischer- 344)	13 wk (W)	Resp	12.5			NTP 1993 NaCN
			Cardio	12.5			
			Hemato	12.5			
			Hepatic	12.5			
			Renal	12.5			
			Endocr	12.5			
			Bd Wt	12.5			

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
14	Rat (NS)	11.5 mo (F)	Endocr		30 M (decreased plasma thyroxine at 4 months; increased thyroid weight at 11 months)		Philbrick et al. 1979 KCN
			Bd Wt			30 M (38% decreased weight gain)	
15	Rat (NS)	11.5 mo (F)	Endocr		67 M (decreased plasma thyroxine and thyroxine secreting rate; increased thyroid weight at 11 mo)		Philbrick et al. 1979 KSCN
			Bd Wt	67 M			
16	Mouse (B6C3F1)	13 wk (W)	Cardio	24.3 M 28.8 F			NTP 1993 NaCN
			Hemato	24.3 M 28.8 F			
			Hepatic	24.3 M 28.8 F			
			Renal	24.3 M 28.8 F			
			Endocr	24.3 M 28.8 F			
			Bd Wt	24.3 M 28.8 F			

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
17	Dog (NS)	14 wk (F)	Cardio			1.04 M (hemorrhage, pyknotic nuclei and swelling of muscle fibers)	Kamalu 1993 Cassava
			Hepatic		1.04 M (periportal vacuolation and congestion)		
			Renal			1.04 M (increased urinary protein, congested kidneys with vacuolation, casts, desquamation, and proximal tubule damage)	
			Endocr			1.04 M (adrenal cortex swelling, hemorrhage, and fibrosis)	
			Metabolic		1.04 M (decreased albumin, Ca & K levels)		
18	Dog (NS)	14 wk (F)	Cardio	1.04 M			Kamalu 1993 NaCN
			Hepatic	1.04 M			
			Renal			1.04 M (increased urinary protein, casts and some desquamation)	
			Endocr		1.04 M (thickening of zona glomerulosa)		
			Metabolic		1.04 M (decreased albumin and K levels)		
19	Pig (Pittman-Moore)	24 wk 7 d/wk 1 x/d (GW)	Gastro	0.4	0.7 (vomiting)		Jackson 1988 KCN
			Endocr		0.4 (T3 and T4 depression)		

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
20	Pig (Yorkshire)	Gd 1-110 (F)	Renal		0.64 F (proliferation of glomerular cells in dams)		Tewe and Maner 1981b KCN & cassava
			Endocr	5.6 F	11.3 F (thyroid gland hypofunction and enlargement in dams)		
	Immunological/Lymphoreticular						
21	Rat (Fischer- 344)	13 wk (W)		12.5			NTP 1993 NaCN
22	Mouse (B6C3F1)	13 wk (W)		24.3 M 28.8 F			NTP 1993 NaCN
	Neurological						
23	Rat (Sprague-Dawley)	90 d 1 x/d (G)			0.14 (hypoactivity and posture hunching)		Gerhart 1987a CuCN
24	Rat (Sprague-Dawley)	90 d 1 x/d (G)			0.8 (hypoactivity)	7.8 (convulsions, lethargy)	Gerhart 1987b KAg(CN)2
25	Rat (Fischer- 344)	13 wk (W)		12.5			NTP 1993 NaCN
26	Rat (NS)	11.5 mo (F)				30 M (modest myelin degeneration in spinal cord)	Philbrick et al. 1979 KCN
27	Rat (NS)	11.5 mo (F)				67 M (modest myelin degeneration in spinal cord)	Philbrick et al. 1979 KSCN

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to[a] figure	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
28	Mouse (B6C3F1)	13 wk (W)		24.3 M 28.8 F			NTP 1993 NaCN
29	Pig (Pittman-Moore)	24 wk 7 d/wk 1 x/d (GW)			0.4 (reduced exploratory, increased victimization behavior)		Jackson 1988 KCN
	Reproductive						
30	Rat (Sprague-Dawley)	90 d 1 x/d (G)		4.35	14.5 (increased testes weight)		Gerhart 1987a CuCN
31	Rat (Sprague-Dawley)	90 d 1 x/d (G)		0.8	2.6 (increased gonadal weight in males)		Gerhart 1987b KAg(CN)2
32	Rat (Fischer- 344)	13 wk (W)		4.5[b] M 12.5 F	12.5 M (decreased left epididymal (7%), left caudal epididymal (13%), & testes weights (8%), number of spermatid heads per testis (14%), & spermatid count (14%))		NTP 1993 NaCN
33	Mouse (B6C3F1)	13 wk (W)		8.6 M 28.8 F	24.3 M (10 and 18% decrease in left epididymus and caudal epididymus weights)		NTP 1993 NaCN

Table 2-2. Levels of Significant Exposure to Cyanide - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
33	Mouse (B6C3F1)	13 wk (W)		8.6 M 28.8 F	24.3 M (10 and 18% decrease in left epididymus and caudal epididymus weights)		NTP 1993 NaCN
34	Dog (NS)	14 wk (F)				1.04 M (reduced spermatogenesis cycle, germ cell sloughing and degeneration)	Kamalu 1993 NaCN
35	Dog (NS)	14 wk (F)				1.04 M (occasional abnormal cells and seminiferous tubules devoid of normal germ cells)	Kamalu 1993 Cassava
	Developmental						
36	Rat (Wistar)	Gd 1-16 or 1-20 Ld 1-21 (F)		1.2	51 (decreased growth in pups)		Tewe and Maner 1981a KCN

[a] The number corresponds to entries on Figure 2-2.

[b] Used to derive intermediate oral minimal risk level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; $CA(CN)_2$ = calcium cyanide; CN = cyanide ion; CuCN = copper cyanide; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; HCN = hydrogen cyanide; Hemato = hematological; incr = increased; $KAgCN_2$ = potassium silver cyanide; KCN = potassium cyanide; KSCN = potassium thiocyanate; Ld = lactation day; LD_{50} = lethal dose, 50% kill; LD_{Lo} = lowest lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; NTP = National Toxicology Program; Resp = respiratory; SDH = sorbital dehydrogenase; (W) = water; wk = week(s); x = times

Figure 2-2. Levels of Significant Exposure to Cyanide - Oral

Acute (≤14 days)

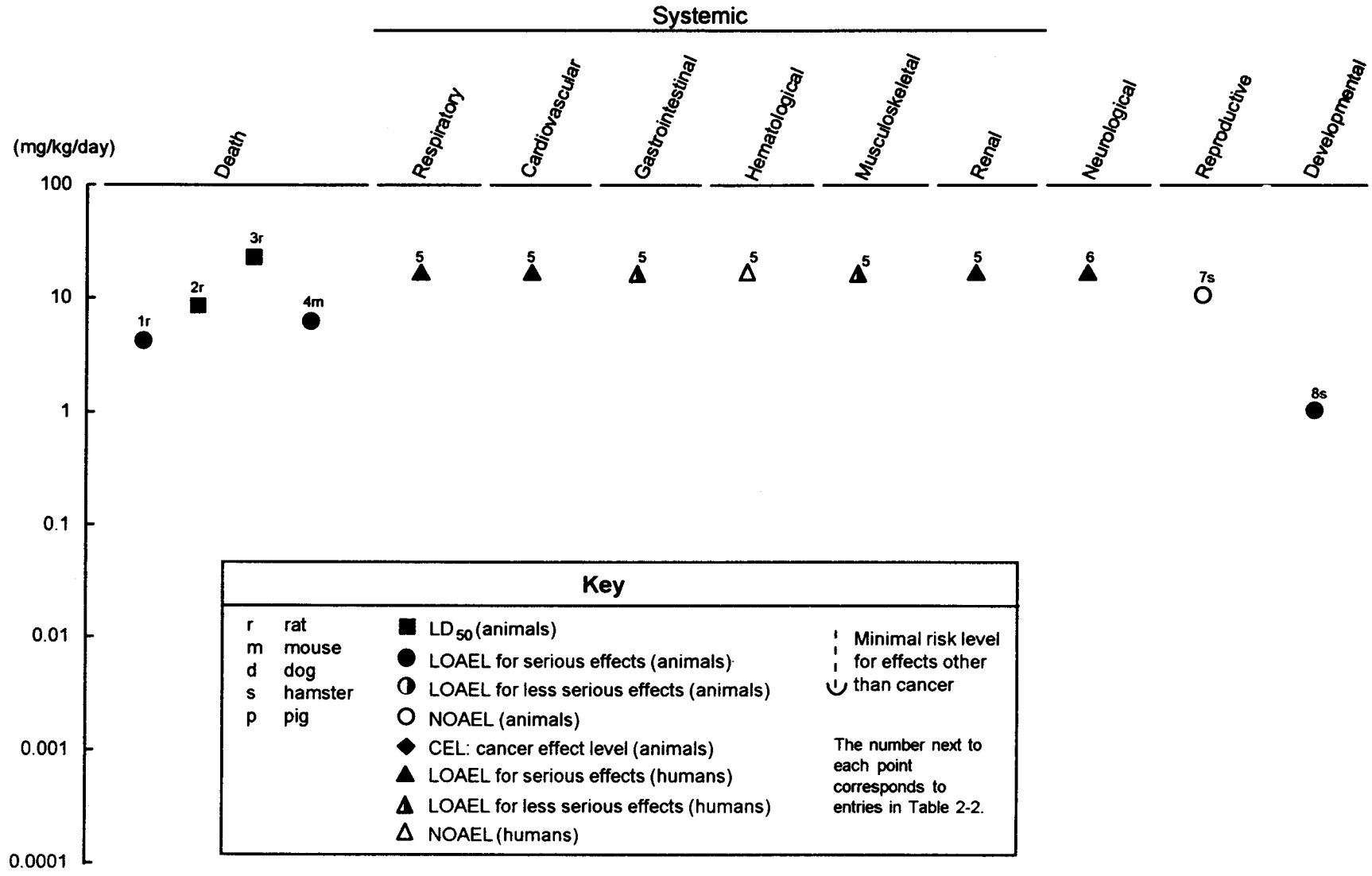


Figure 2-2. Levels of Significant Exposure to Cyanide - Oral (cont.)

Intermediate (15-364 days)

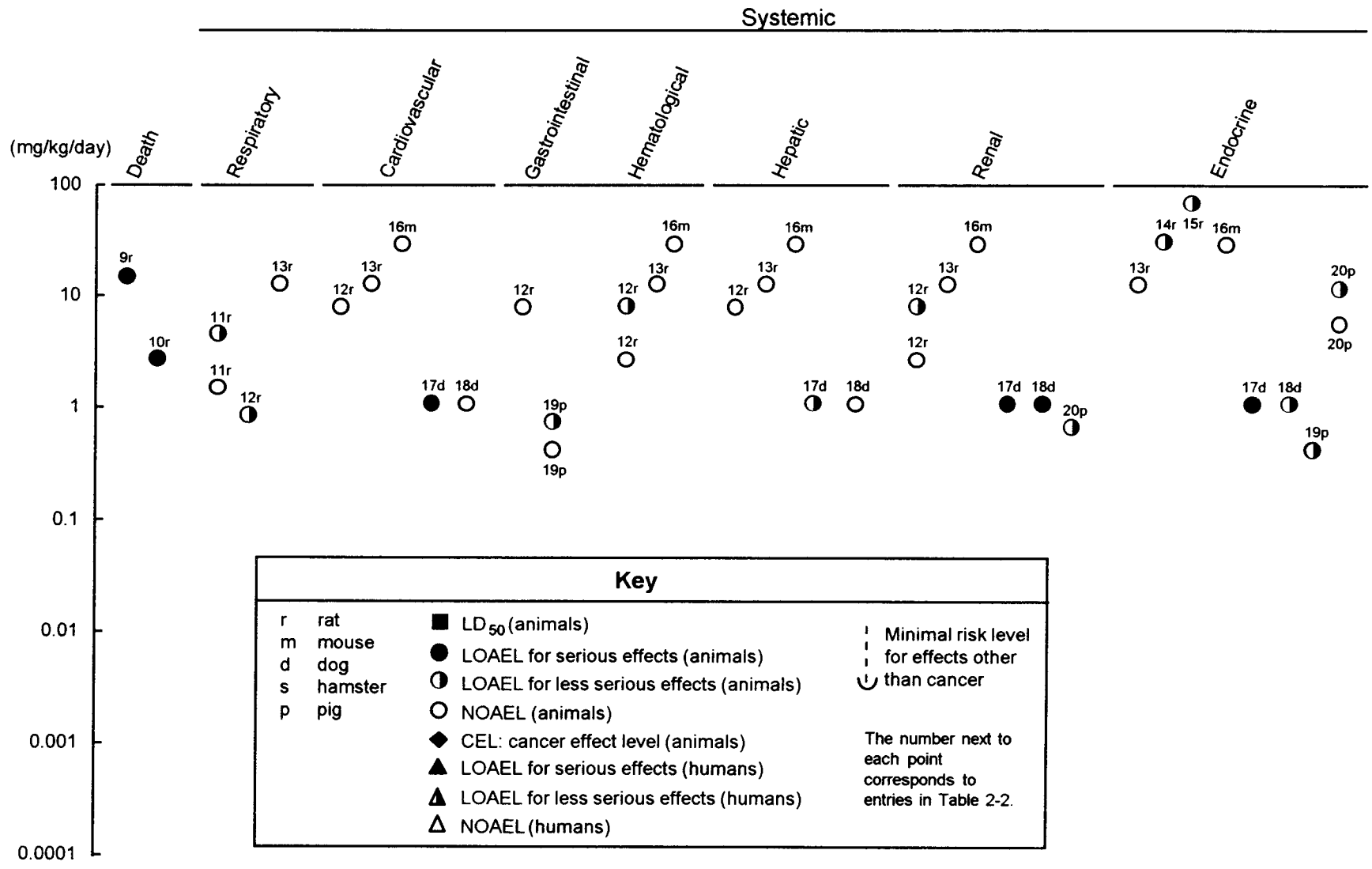
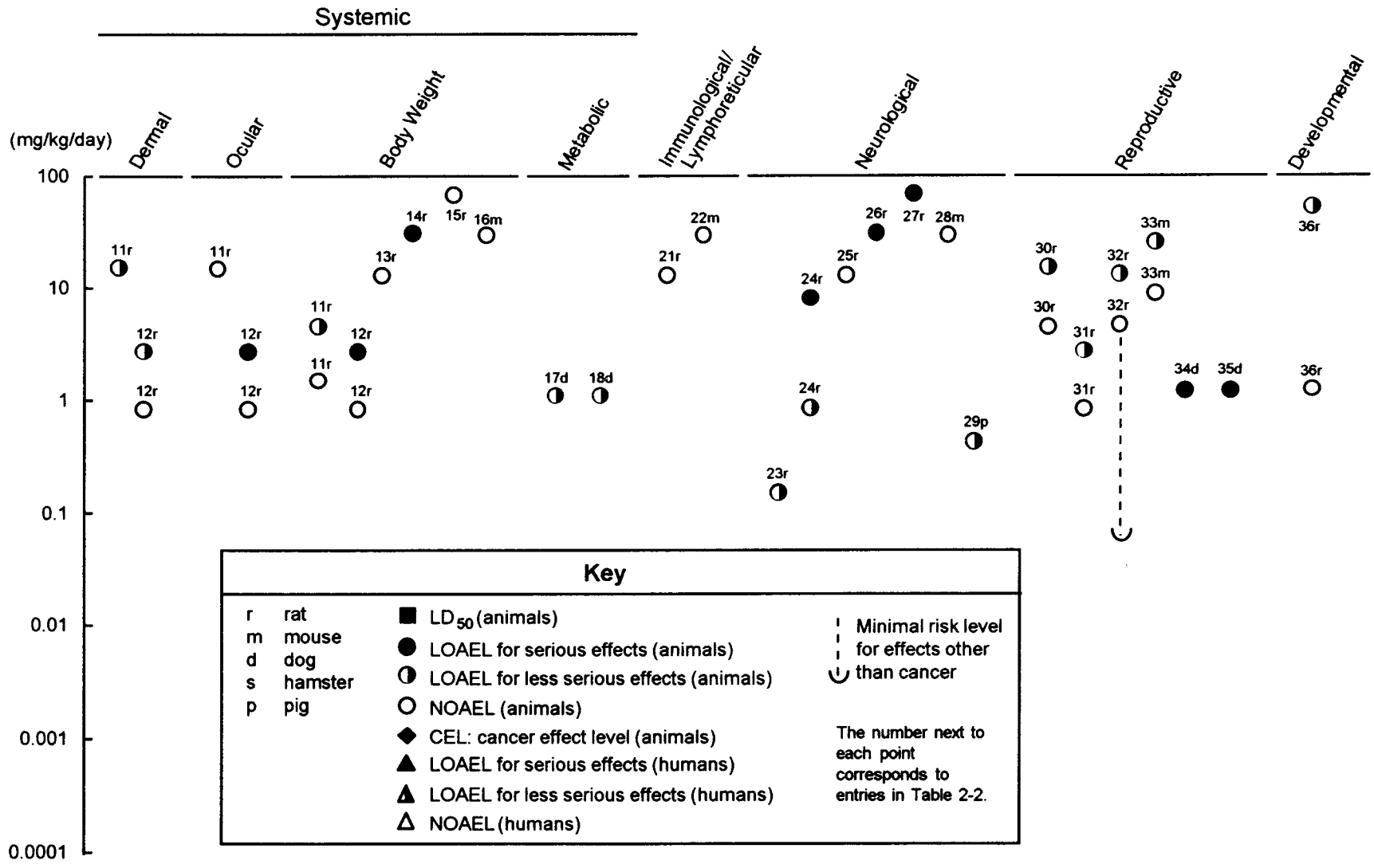


Figure 2-2. Levels of Significant Exposure to Cyanide - Oral (cont.)

Intermediate (15-364 days)



2.2.2.2 Systemic Effects

The systemic effects observed in humans and animals after oral exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Breathing irregularities occur after cyanide poisoning through oral exposure. Stertorous, deep, and rapid breathing was reported in a man who ingested ≈ 15 mg CN^-/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948). Shortness of breath and dyspnea were observed in 2 reports of suicide attempts; one man ingested 7.6 mg CN^-/kg (Goodhart 1994) and the other man ingested 0.57 mg CN^-/kg (Saincher et al. 1994), both as potassium cyanide. A man admitted to a hospital after ingesting an unknown amount of sodium cyanide ceased breathing (Grandas et al. 1989). Tachypnea was also reported in children who were poisoned by cyanide after ingesting apricot pits (Lasch and El Shawa 1981).

Respiratory effects were also observed in animals exposed to cyanide. Labored respiration was reported in rats treated with 4.35 mg CN^-/kg/day as copper cyanide by gavage for 90 days (Gerhart 1987a). No effects were reported at 1.45 mg CN^-/kg/day. Labored respiration occurred in rats exposed at a lower dose of 0.8 mg CN^-/kg/day when administered in a form of potassium silver cyanide for 90 days (Gerhart 1987b). Lung congestion and hemorrhage seen at necropsy were attributed to asphyxia rather than to a direct effect of cyanide. In another study, rats were exposed to 0.2-12.5 mg CN^-/kg/day as sodium cyanide in the drinking water for 13 weeks. Changes in absolute lung weight were seen, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). No respiratory effects were reported in rats exposed to a target dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have been considerably lower than 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Cardiovascular Effects. Several case studies reported cardiovascular effects in humans after oral exposure to cyanide. Weak and shallow pulse, and inaudible heart sounds were observed in a comatose man on hospital admission after ingestion of ≈ 15 mg CN^-/kg as potassium cyanide (Liebowitz and Schwartz 1948). Following gastric lavage and glucose infusion, the pulse rate and blood pressure became elevated. An enlarged heart was noted. No cardiovascular effects were reported during the recovery. In another study, children poisoned by apricot pits had hypotension upon hospital admission (Lasch and El Shawa 1981).

2. HEALTH EFFECTS

After intermediate- or chronic-duration oral exposure to inorganic cyanides, cardiovascular effects in animals, if any, are minimal. No significant histopathological changes were observed in rats exposed to 2.6 or 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). Changes in absolute heart weight were seen in male and female mice exposed to 0.3-28.8 mg CN^-/kg/day as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Dogs fed a diet of cassava ingested 1.04 mg CN^-/kg/day for 14 weeks and exhibited hemorrhage, pyknotic nuclei, and swelling of muscle fibers in the myocardium, while dogs fed rice to which 1.04 mg CN^-/kg food was added as sodium cyanide did not show any cardiovascular effects (Kamalu 1993). Furthermore, no cardiovascular effects were observed in rats exposed to an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have differed from 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Gastrointestinal Effects. Solutions of sodium and potassium cyanide are alkaline and, as such, can cause corrosive responses in the stomach following ingestion. Vomiting was reported in children who ingested a large number of apricot pits (Lasch and El Shawa 1981) and in a man who ingested 7.6 mg CN-/kg in a suicide attempt (Goodhart 1994). Gastrointestinal spasms were reported in a man who accidentally ingested (and inhaled) an unknown amount of potassium cyanide (Thomas and Brooks 1970). Gastric surgery for extensive necrosis had to be performed in a man after he ingested an unknown amount of sodium cyanide (Grandas et al. 1989).

Diarrhea was observed in rats treated orally with 14.5 mg CN^-/kg/day copper cyanide for 90 days (Gerhart 1987a). No effects were observed at 4.35 mg/kg/day. However, the diarrhea was probably due to the toxicity of copper. No gastrointestinal effects were found in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). However, increased vomiting was reported in fasted pigs in a dose as low as 0.7 mg CN^-/kg/day given as potassium cyanide for 24 weeks by gavage; however, these animals were experimentally compromised as they were starved (Jackson 1988). Chronic intestinal inflammation occurred in dogs exposed to 20.27 mg CN^-/kg/day for 14.5 months (Hertting et al. 1960).

Hematological Effects. Information regarding hematological effects in humans after oral exposure to cyanide is limited. No adverse hematologic effects were reported in a man who ingested 15 mg CN-/kg as potassium cyanide (Liebowitz and Schwartz 1948).

2. HEALTH EFFECTS

In animals, hematological effects were observed in studies with copper cyanide, potassium silver cyanide, and sodium cyanide. Hemolytic anemia was diagnosed in the group of rats treated by gavage for 90 days with 14.5 mg CN^-/kg/day as copper cyanide (Gerhart 1987a). Decreased erythrocytes were reported together with decreased hemoglobin concentrations and decreased hematocrit. The diagnosis of anemia was supported by microscopic findings of pigmentation of the spleen and liver, presence of hemoglobin in the cytoplasm of the renal convoluted tubule epithelium, and by hyperplasia of hematopoietic tissue (spleen and bone marrow). Decreased hemoglobin was observed also at 4.35 mg CN^-/kg/day. Hemolytic anemia is characteristic of copper toxicity; therefore, the hematological effects can be attributed to copper toxicity rather than to cyanide toxicity. Increased mean corpuscular volume, mean corpuscular hemoglobin concentration, and spleen weight indicated hematological effects in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days by gavage. No effects were found at 2.6 mg CN^-/kg/day (Gerhart 1987b). The contribution of silver to the hematological effects is not known. In another study, minimal changes were observed in hematology in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks and the authors did not consider them to be treatment related (NTP 1993).

Musculoskeletal Effects. Muscular rigidity was observed in humans after acute cyanide poisoning (Grandas et al. 1989) and rhabdomyolysis, a clinical syndrome characterized by skeletal muscle injury, was observed in a man who ingested 0.57 mg CN^-/kg/day in a suicide attempt (Saincher et al. 1994). No studies were located regarding musculoskeletal effects in animals after oral exposure to cyanide.

Hepatic Effects. Increased serum creatinine and serum creatinine kinase were observed in a man who ingested 0.57 mg CN^-/kg/day in a suicide attempt (Saincher et al. 1994).

In animals, hepatotoxicity was observed after ingestion of copper cyanide. Male rats treated for 90 days by gavage with 14.5 mg CN^-/kg/day as copper cyanide had increased levels of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels, increased bilirubin and alkaline phosphatase, and decreased globulin levels in the blood (Gerhart 1987a). Liver necrosis was observed in the group of female rats treated with 4.35 mg CN^-/kg/day. However, blood chemistry did not reveal any changes. The hepatic effects of copper cyanide are probably due to the toxicity of copper rather than of cyanide.

2. HEALTH EFFECTS

Changes in absolute and relative liver weights were reported in rats exposed to 0.2-12.5 mg CN^-/kg/day and mice exposed to 0.3-28.8 mg CN^-/kg/day, both as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). In another study, periportal vacuolation and congestion were observed in the livers of dogs fed 1.04 mg CN-/kg/day, as cassava, while no hepatic effects were observed in dogs fed rice containing the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993). No hepatic effects were reported in rats exposed by gavage to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b) or in rats exposed to an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have differed from 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food.

Renal Effects. Information regarding renal effects of cyanide in humans is limited to one report. Albuminuria was found in a man during the first 2 days after ingestion of 15 mg CN-/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948).

In animals, decreased kidney weight was observed in rats treated with 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1987a). No changes were reported at 4.35 mg/kg/day exposure. However, copper toxicity was probably responsible for the kidney effects. Increased blood urea nitrogen was found at 7.8 mg CN^-/kg/day, but not at 2.6 mg CN^-/kg/day, as potassium silver cyanide (Gerhart 1987b). The contribution of silver to this effect is not known. No significant changes indicating renal effects were found on analysis of blood samples taken at the end of the experiment. Changes in absolute and relative kidney weights were observed in rats and mice exposed to 0.2-12.5 mg CN-/kg/day and mice exposed to 0.3-28.8 mg CN^-/kg/day, both as sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993).

Histopathologically, a proliferation of glomerular cells in the kidney was observed in pigs exposed to 0.64 mg CN^-/kg/day in cassava feed for 110 days (Tewe and Maner 1981b). In another study, vacuolation, swelling, and proximal tubule damage with desquamation of the epithelium and casts were observed in kidneys of dogs fed 1.04 mg CN^-/kg/day as cassava, while increased urinary protein, casts, and some desquamation, but no damage in proximal tubules, were observed in dogs fed rice with the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993). However, no renal effects were observed in rats exposed to an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955); in this study, however, the actual dose may have been different due to evaporation of hydrogen cyanide from the food. Cloudy swelling of epithelial cells of

renal tubules was reported in 3 dogs; each dog was exposed to a different dose of sodium cyanide (ranging from 0.27 to 1.68 mg CN^-/kg/day) for 14.5 months (Hertting et al. 1960).

Endocrine Effects. Cyanide occurs naturally in several plants, such as cassava, soybeans, spinach, and bamboo shoots, in which it is generated after ingestion from cyanogenic glycosides. Chronic oral exposure to cyanide in humans who eat cassava as a main carbohydrate source of their diet has been associated with thyroid toxicity. The effects are probably caused by thiocyanate, a metabolite of cyanide which reduces iodine uptake by the thyroid. The incidence of endemic goiter correlated with cassava intake in the Congo, where thyroid uptake of radioiodine was decreased in the goitrous area, compared with the controls (Delange and Ermans 1971). In another study, decreased FT41 and increased FT31 levels, T_3/T_4 ratio, and TSH were measured in a cohort from a village where an epidemic of spastic paraparesis was found. However, the incidence of endemic goiter was not elevated in this village. Examined individuals also had very high levels of thiocyanate in serum and urine (Cliff et al. 1986).

Thyroid effects were also found in animals exposed to cyanide. Rats fed a diet containing 30 mg CN^-/kg/day as potassium cyanide for 4 months had a significant decrease in plasma thyroxine levels and thyroxine secretion rates; at 11 months, treated rats showed no significant decreases in thyroxine concentrations, but had significant increases in relative thyroid weight (Philbrick et al. 1979). When pigs were fed a diet containing potassium cyanide and/or cassava roots during pregnancy, an increase in the maternal thyroid weight and thyroid gland hypofunction were observed after ingestion of 11.3 mg CN^-/kg/day (Tewe and Maner 1981b). No effects on the thyroid gland were found at 5.6 mg CN^-/kg/day. In another study, no effects on the thyroid gland were noted at 12.5 mg CN^-/kg/day in rats given sodium cyanide in drinking water for 13 weeks or in mice given 24.3-28.8 mg CN^-/kg/day (NTP 1993). However, thyroid effects have been reported at low doses in another study. Decreased thyroid function was found in fasted pigs exposed to 0.4 mg CN^-/kg/day as potassium cyanide for 24 weeks by gavage; however, the animals were experimentally compromised as they were starved (Jackson 1988).

Effects on the adrenal gland, including swelling of the adrenal cortex, hemorrhage, and fibrosis, were observed in dogs fed 1.04 mg CN^-/kg/day as cassava, as well as in dogs fed rice with the same concentration of cyanide, as sodium cyanide, for 14 weeks (Kamalu 1993).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to cyanide.

2. HEALTH EFFECTS

During intermediate-duration exposure, discolored inguinal fur was found in rats exposed for 90 days to 14.5 mg CN^-/kg/day by gavage as copper cyanide (Gerhart 1987a) and to 2.6 mg CN^-/kg/day as potassium silver cyanide (Gerhart 1987b).

Ocular Effects. Macular degeneration and optic atrophy were reported in humans who ingested cassava containing an unknown concentration of cyanide (van Heijst et al. 1994).

Ocular opacity was noted in rats exposed to 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). No pathological findings were observed during ophthalmological examination of rats exposed to 14.5 mg CN^-/kg/day as copper cyanide for 90 days (Gerhart 1987a).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to cyanide.

Decreased body weight gain was cited as one of the effects of exposure to copper cyanide and potassium silver cyanide. The effect was reported in male rats exposed for 90 days to 4.35 mg CN^-/kg/day as copper cyanide, but not in those exposed to 1.45 mg CN^-/kg/day for 90 days (Gerhart 1987a). Furthermore, decreased weight gain was found in male rats exposed to 2.6 mg CN^-/kg/day as potassium silver cyanide for 90 days (Gerhart 1987b). The presence of the copper or silver may have contributed to the observed decreased body weight. Pregnant hamsters fed 1 .O mg CN^-/kg/day in cassava for 10 days during gestation had decreased body weight gain (F&es et al. 1986a). No decrease in body weight gain was observed in female rats exposed to 12.5 mg CN^-/kg/day or mice of either sex exposed to 0.3-28.8 mg CN^-/kg/day in drinking water for 13 weeks. A slight decrease in body weight gain was observed in male rats exposed to 0.5 and 12.5 mg CN^-/kg/day (NTP 1993).

MetabolicEffects. Yen et al. (1995) reported metabolic acidosis in 67% of patients acutely poisoned by unknown concentrations of cyanide.

The only study located in animals regarding metabolic effects reported decreased serum albumin and lowered calcium and potassium levels in dogs fed 1.04 mg CN^-/kg/day as cassava or sodium cyanide for 14 weeks (Kamalu 1993)

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to cyanide.

No significant changes in absolute or relative thymus weight were noted in rats and mice exposed to up to 12.5 and 28.8 mg CN^-/kg/day, respectively, in drinking water for 13 weeks (NTP 1993).

2.2.2.4 Neurological Effects

Neurologic toxicity following cyanide ingestions differs depending on length of exposure. Neurological effects of cyanide poisoning in humans may correlate with the amount ingested; however, the exact doses consumed by the victims are usually not known, Tremors were reported in a patient who accidentally ingested an unknown amount of fluid containing 2.3% silver cyanide and 6.9% sodium cyanide (Chen and Rose 1952). Children who ingested a large number of apricot pits experienced various neurological effects ranging in severity from headaches to coma (Lasch and El Shawa 1981). The severity of effects corresponded with the amount of ingested pits. Comatose patients were admitted to a hospital after ingesting 15 mg CN^-/kg (Liebowitz and Schwartz 1948), 7.6 mg CN^-/kg(Goodhart 1994), 114-229 mg CN^-/kg (Kasamo et al. 1993), and 5.7 mg CN^-/kg (Valenzuela et al. 1992), all as potassium cyanide.

Four reports were located regarding development of Parkinsonism in patients after cyanide ingestion. A woman in a light coma had positive Babinski's sign on the right with slight right hemiparesis and dysphonia within 2 weeks after acute cyanide poisoning (Carella et al. 1988). Within 5 years, progressive Parkinsonism, dystonia, and apraxia of the right eye opening was present. Atrophy of the cerebellum and distinct ventricular enlargement in cerebral hemispheres were revealed by computed tomography and magnetic resonance image examinations. In another case, a man went into a coma after ingesting an unknown amount of sodium cyanide (Grandas et al. 1989). Later he regained consciousness, but was apathetic with reduced speech and a loss of balance; dystonia and severe Parkinsonism developed during following years. Computed tomography scan revealed bilateral luciencies in the putamen and external globus pallidus. Severe Parkinsonism also developed in two men who ingested ≈ 5.57 mg CN^-/kg (Utti et al. 1985) and 8.57 mg CN^-/kg (Rosenberg et al. 1989), respectively, as potassium cyanide in suicide attempts. Lesions were reported in the globus pallidus and putamen in both cases. However, it must be noted that these studies do not demonstrate a true cause and effect relationship between cyanide exposure and Parkinsonism. In addition, other chemicals, such as manganese and carbon monoxide, and therapy with certain drugs may result in Parkinsonism

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The effects of chronic oral exposure of humans to cyanogenic glucosides were studied in regions of Africa with populations that consume a high level of cassava roots (Howlett et al. 1990; Ministry of Health, Mozambique 1984; Monekosso and Wilson 1966; Money 1958; Osuntokun 1968, 1972; Osuntokun et al. 1969; Tylleskar et al. 1994). In some cases, the diet consisted almost exclusively of cassava roots, due to failure of other food crops (Howlett et al. 1990). A variety of neuropathies have been observed in these regions and the findings correlated with increased blood thiocyanate levels, all collectively termed "tropical ataxic neuropathy" (Osuntokun 1973). Symmetrical hyperreflexia of the upper limbs, symmetrical spastic paraparesis of the lower limbs, spastic dysarthria, diminished visual acuity, peripheral neuropathy, cerebellar signs, and deafness were among the clinical findings (Ministry of Health, Mozambique 1984). Decreased plasma vitamin B_{12} levels were also detected in affected individuals (Monekosso and Wilson 1966). Konzo, a distinct upper motor neuron disease characterized by the sudden onset of varying degrees of symmetric, isolated, nonprogressive spastic paraparesis, has occurred in rural areas of Africa and has been associated with high dietary cyanide exposure from the consumption of insufficiently processed bitter cassava (Tylleskar et al. 1994). However, a recent study reported the isolation of scopoletin, a potent hypotensive and spasmolytic agent, from cassava roots (Obidoa and Obasi 1991). This substance, which remains in cassava during processing, rather than cyanide, was suggested to be the etiological agent in the tropical ataxic neuropathy observed among cassava eaters (Obidoa and Obasi 1991). In addition, protein and vitamin deficiencies may subject people in the tropics who eat cassava to increased risks of tropical neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969).

The central nervous system is also a primary target of orally administered cyanide in animals. Tremors, convulsions, recumbency, and lethargy were observed in rats exposed to 7.8 mg CN^-/kg/day as potassium silver cyanide for 90 days by gavage (Gerhart 1987b). Since 28 of 40 rats died at this dose level, some of the effects described may represent nonspecific signs that precede death. Hypoactivity was observed in all exposed groups starting at a dose of 0.8 mg CN^-/kg/day. Similarly, hypoactivity was reported in rats exposed to ≥0.14 mg CN^-/kg/day as copper cyanide for 90 days by gavage. At 4.35 mg CN-/kg/day, fixed posture occurred, while pronounced lethargy was noted at 14.5 mg CN^-/kg/day. Decreased brain weight was reported at 14.5 mg CN^-/kg/day cyanide (Gerhart 1987a). The severity of effects increased as the dose increased in both of these studies and males seemed to be more sensitive to cyanide toxicity than females. However, silver and/or copper toxicity may have contributed to the observed effects in both of these studies.

2. HEALTH EFFECTS

Rats fed a diet containing 30 mg CN^-/kg/day as potassium cyanide and 67 mg CN^-/kg/day as thiocyanate for 11.5 months had myelin degeneration in the spinal cord (Philbrick et al. 1979). In a behavioral study, exposure to 0.4 mg CN^-/kg/day as potassium cyanide by gavage for 24 weeks in fasted pigs led to slower reaction time, reduced exploratory behavior, and increased victimization behavior in pigs however, the animals were experimentally compromised as they were starved (Jackson 1988). In contrast, no neurological effects were reported in rats fed an estimated dose of 10.4 mg CN^-/kg/day as hydrogen cyanide in their feed for 2 years (Howard and Hanzal 1955). The actual dose, however, may have been considerably lower than 10.4 mg/kg/day due to evaporation of hydrogen cyanide from the food. No histopathological changes to the brain were noted in rats and mice exposed to up to 12.5 and 28.8 mg CN^-/kg/day, as the sodium salt, respectively, in the drinking water for 13 weeks (NTP 1993). Degenerative changes in ganglion cells were reported in 3 dogs that were exposed to 0.27-l .68 mg CN^-/kg/day as sodium cyanide in capsules for 14.5 months (Hertting et al. 1960).

The highest NOAEL value and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to cyanide.

Increased early embryonic deaths were reported in rats fed a diet containing 80% cassava powder during gestation, but no reproductive effects were found in a group fed with 50% cassava powder (Singh 198 1). Furthermore, no changes were observed in the number of implantations or resorptions in hamsters fed a cassava diet that provided 10.4 mg CN-/kg/day during gestation (Frakes et al. 1986a*).* Increased gonadal weight was observed in male rats exposed to 14.5 mg CN^-/kg/day as copper cyanide (Gerhart 1987a) or 2.6 mg CN^-/kg/day as potassium silver cyanide, for 90 days (Gerhart 1987b). The NOAEL values were 4.35 mg CN^-/kg/day (Gerhart 1987a) and 0.8 mg CN^-/kg/day (Gerhart 1987b), respectively. No effects were observed in female rats in either study. A reduction in the spermatogenic cycle, testicular germ cell sloughing and degeneration, and occasional abnormal cells were noted in dogs fed 1.04 mg CN^-/kg/day as cassava and in dogs fed rice containing the same concentration of cyanide, as sodium cyanide for 14 weeks (Kamalu 1993).

A number of reproductive effects were observed following exposure of rats and mice to sodium cyanide in the drinking water for 13 weeks (NTP 1993). In male rats, reproductive effects including decreased left

epididymis weight, left cauda epididymis weight, left testis weight, spermatid heads, and spermatid counts were observed at 12.5 mg CN^-/kg/day. In female rats, significantly more time was spent in proestrus and diestrus stages, and less time was spent in estrus and metestrus stages in the 4.9 and 12.5 mg CN^-/kg/day groups. In male mice, a significant decrease in the left epididymal and caudal epididymal weights was noted at 24.3 mg CN^-/kg/day, but no changes in sperm motility or spermatid head density were observed. No changes were noted on the estrus cycle length in female mice. This study was used as the basis for the oral intermediate MRL as described in the footnote to Table 2-2 and in Appendix A.

The highest NOAEL value and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to cyanide. Developmental abnormalities (microcephaly with open eyes, limb defects, and growth retardation) were observed in 28% of the fetuses of rats exposed to feed containing 80% cassava powder during gestation (Singh 1981). Teratogenic effects (encephalocele and rib abnormalities) were reported in hamsters exposed to a single oral dose of amygdalin during gestation, but these changes were found only at maternally toxic doses (Willhite 1982). Fetotoxicity (reduced fetal weight and ossification) were found in the offspring of hamsters fed a cassava diet providing 1 .O mg CN^-/kg/day during pregnancy (Frakes et al. 1986a) or to the cyanogenic glucoside linamarin at 120 or 140 mg/kg (Frakes et al. 1985). Blood cyanide increased to a peak of 110 nmol/mL at 3 hours after such a dose of linamarin or to 140 nmol/mL after amygdalin (Frakes et al. 1986b). In contrast, no major developmental effects were observed in rats that were fed a basal cassava diet providing ≈ 1.2 mg CN^-/kg/day or in rats whose cassava feed was supplemented with potassium cyanide bringing the total dose to 51 mg CN^-/kg/day, (assuming young growing rats and pregnant rats consume food each day equivalent to 10% of their body weight) (Tewe and Maner 1981a). The rats were exposed to cyanide during gestation days 16-20 and then for 21 days during lactation. When their offspring were exposed to similar diets providing doses of ≈ 1.2 and 51 mg CN^-/kg/day, decreased growth was observed in the higher dosed weanlings regardless of the exposure *in utero.* When pigs were fed a cassava diet alone or one supplemented with potassium cyanide for 110 gestation days, no effects on number of fetuses or upon fetal weight were observed in the 11.3-mg CN^-/kg/day cyanide exposed group (Tewe and Maner 1981b).

The highest NOAEL value and all reliable LOAEL values for developmental effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to cyanide.
A single oral dose of 1-mg CN^-/kg as potassium cyanide did not inhibit testicular deoxyribonucleic acid

(DNA)-synthesis in mice (Friedman and Staub 1976). Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer effects in humans or animals after oral exposure to cyanide.

2.2.3 Dermal Exposure

Chronic dermal exposure of humans to cyanide can occur in occupational settings. However, the main route of exposure is considered to be inhalation and, therefore, the occupational exposure studies are discussed in Section 2.2.1.

2.2.3.1 Death

An average LD_{50} value for dermal exposure of 100 mg CN^-/kg as hydrogen cyanide was estimated for humans (Rieders 1971). Blood cyanide greater than 0.2 µg/mL may be associated with acute signs of cyanide poisoning and deaths occur after blood cyanide reaches 1 µg/mL (Snodgrass 1996).

LD_{50} values were calculated for dermal exposure to cyanides in rabbits; 6.7 mg CN^-/kg when applied as hydrogen cyanide, 7.7 mg CN^-/kg as sodium cyanide, and 8.9 mg CN^-/kg as potassium cyanide (Ballantyne 1983a). Moistening the skin slightly lowered, and abrading the skin substantially lowered, the dermal LD_{50} of cyanide as sodium cyanide (Ballantyne 1988). Similar differences in toxicity of various chemical forms of cyanide were observed after cyanide was applied to the inferior conjunctival sac of one eye (Ballantyne 1983a, 1983b, 1988). Transocular LD_{50}, values were 1.0 mg CN^-/kg as hydrogen cyanide, 2.68 mg CN^-/kg as sodium cyanide, and 3.2 mg CN^-/kg as potassium cyanide. The deaths occurred within

3-12 minutes. Deaths occurred also in guinea pigs when their skin was exposed to hydrogen cyanide, however, the doses could not be quantified (Fairley et al. 1934; Walton and Witherspoon 1926). The LD,, values for death are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal or hepatic effects in humans or animals after dermal exposure to cyanide. The systemic effects observed in humans and animals after dermal exposure to cyanide are discussed below. The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration category are recorded in Table 2-3.

Respiratory Effects. Breathing irregularities including Cheyne-Stokes respiration developed in two persons who fell into cisterns containing copper cyanide or potassium cyanide (Dodds and McKnight 1985; Trapp 1970) or whose hands were exposed to hydrogen cyanide (Potter 1950). The effects reflect the central nervous system toxicity of cyanide.

Rapid breathing was reported as the first sign of toxicity in rabbits that received 0.9 mg CN‘/kg as hydrogen cyanide, 1.69 and 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide in their conjunctival sacs (Ballantyne 1983b, 1988). Similarly, labored or rapid breathing preceded coma and death in guinea pigs exposed dermally to unknown doses of hydrogen cyanide (Fairley et al. 1934; Walton and Witherspoon 1926).

Cardiovascular Effects. Peripheral vasoconstriction and gross plasma extravasation were reported in a man who accidentally fell into a cistern with hot copper cyanide (Dodds and McKnight 1985). Palpitations were recorded in 3 men who wore respiratory masks while working in an atmosphere containing 20,000 ppm hydrogen cyanide for 8-10 minutes (Drinker 1932). The masks were reported to give excellent respiratory protection. Therefore, the effects seen in these men may have been due to dermal exposure.

No studies were located regarding cardiovascular effects in animals after dermal exposure to cyanide.

Table 2-3. Levels of Significant Exposure to Cyanide - Dermal

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL		Reference Chemical Form
				Less Serious	Serious	
ACUTE EXPOSURE						
Death						
Rabbit (NS)	once				8.9 mg/kg F (dermal LD_{50})	Ballantyne 1983a KCN
Rabbit (NS)	once				6.7 mg/kg F (dermal LD_{50})	Ballantyne 1983a HCN
Rabbit (NS)	once				7.7 mg/kg F (dermal LD_{50})	Ballantyne 1983a NaCN
Rabbit (albino)	once				3.2 mg/kg F (transocular LD_{50})	Ballantyne 1983a, 1983b KCN
Rabbit (albino)	once				1.0 mg/kg F (transocular LD_{50})	Ballantyne 1983a, 1983b HCN
Rabbit (New Zealand)	once				4.1 mg/kg F (dermal LD_{50} -abraded skin)	Ballantyne 1988 NaCN
Rabbit (New Zealand)	once				6.3 mg/kg F (dermal LD_{50} -moist skin)	Ballantyne 1988 NaCN
Rabbit (New Zealand)	once				2.4 mg/kg F (transocular LD_{50})	Ballantyne 1988 NaCN
Systemic						
Human	8-10 min	Cardio		20000 ppm M (palpitations)		Drinker 1932 HCN

Table 2-3. Levels of Significant Exposure to Cyanide - Dermal (continued)

Species/ (Strain)	Exposure/ Duration/ Frequency/ (Specific Route)	System	NOAEL	LOAEL			Reference Chemical Form
				Less Serious	Serious		
Rabbit (albino)	once	Resp		2.5 mg/kg F (rapid breathing)			Ballantyne 1983b KCN
		Ocular			2.5 mg/kg F	(corneal opacity, keratitis)	
Rabbit (albino)	once	Resp		0.9 mg/kg F (rapid breathing)			Ballantyne 1983b HCN
		Ocular			0.9 mg/kg F	(corneal opacity, keratitis)	
Rabbit (albino)	once	Resp	1.69 mg/kg F	2.1 mg/kg F (rapid breathing)			Ballantyne 1983b NaCN
		Ocular	1.69 mg/kg F		2.1 mg/kg F	(corneal opacity, keratitis)	
Neurological							
Human	8-10 min			20,000 ppm M (dizziness, weakness, headache)			Drinker 1932 HCN
Rabbit (albino)	once				0.9 mg/kg F	(convulsions and loss of consciousness)	Ballantyne 1983b HCN
Rabbit (New Zealand)	once				2.5 mg/kg F	(convulsions and loss of consciousness)	Ballantyne 1983b KCN
Rabbit (albino)	once		1.7 mg/kg F		2.1 mg/kg F	(convulsions and loss of consciousness)	Ballantyne 1983b NaCN

Cardio = cardiovascular; d = day(s); F = female; HCN = hydrogen cyanide; KCN = potassium cyanide; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed- adverse-effect level; M = male; min = minutes; NaCN = sodium cyanide; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory

2. HEALTH EFFECTS

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to cyanide.

Acute dermal exposure of guinea pigs to an unknown concentration of hydrogen cyanide resulted in submucous hemorrhages in the stomach as observed at necropsy (Fairley et al. 1934).

Renal Effects. The information regarding renal effects following dermal exposure to cyanide in humans is limited to one case report. Transitory oliguria (scanty urination) was observed in a patient who accidentally fell into a cistern containing 1,000 gallons of hot copper cyanide and remained there for 3 minutes before being rescued (Dodds and McKnight 1985).

No studies were located regarding renal effects in animals after dermal exposure to cyanide.

Dermal Effects. No studies were located regarding dermal effects in humans after dermal exposure to cyanide.

When the skin of rabbits was exposed to 5,000 ppm cyanide as cyanogen for 8 hours, no dermal lesions were found (McNerney and Schrenk 1960). Vascular congestion was reported in the skin of guinea pigs after exposure to unknown doses of hydrogen cyanide for 65 minutes (Fairley et al. 1934).

Ocular Effects. No studies were located regarding ocular effects in humans after dermal exposure to cyanide.

Cyanide toxicity was tested in rabbits by applying 1.69-5.28 mg CN^-/kg/day as sodium cyanide to the inferior conjunctival sac of one eye (Ballantyne 1983b, 1988). Irritation, lacrimation, and conjunctival hyperemia were present immediately after the treatment. Keratitis developed in some rabbits after a cyanide application of 0.9 mg CN^-/kg as hydrogen cyanide, 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to cyanide.

2.2.3.4 Neurological Effects

Deep coma developed in two persons who accidentally fell into cisterns containing copper cyanide (Dodds and McKnight 1985) and potassium cyanide, respectively (Trapp 1970). Similarly, a worker, whose hand was exposed to liquid hydrogen cyanide, fell into a coma, lost deep reflexes, and showed dilated pupils within 5 minutes (Potter 1950). Men working in an atmosphere containing 20,000 ppm hydrogen cyanide for 8-10 minutes experienced dizziness, weakness, and headaches (Drinker 1932). The workers wore masks that were reported to give excellent respiratory protection. However, exposure to such high concentrations is not safe because the gas is absorbed through the unprotected skin. The effects seen in these men may have been due to dermal exposure.

Weak and ataxic movements, convulsions, and coma developed in rabbits that received 0.9 mg CN^-/kg as hydrogen cyanide, 2.1 mg CN^-/kg as sodium cyanide, and 2.5 mg CN^-/kg as potassium cyanide into their conjunctival sacs (Ballantyne 1983b, 1988). Rabbits exposed dermally to 1.92 mg CN^-/kg as hydrogen cyanide, 4.0 mg CN^-/kg as potassium cyanide or 2.6 mg CN^-/kg as sodium cyanide exhibited tremors, retrocolic spasms, and convulsions (Ballantyne 1994). Similarly, convulsions and coma preceded death in guinea pigs exposed dermally to unknown doses of hydrogen cyanide (Fairley et al. 1934; Walton and Witherspoon 1926).

All reliable LOAEL values for neurological effects in each species for acute duration are recorded in Table 2-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to cyanide:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans or animals after dermal exposure to cyanide.

2. 3 TOXICOKINETICS

Cyanide gas and certain salts are rapidly absorbed following inhalation, oral, and dermal exposure. Following inhalation, it is rapidly distributed throughout the body, with measurable levels detected in all organs studied to date. Cyanide can be distributed in the body within seconds and death can occur within minutes. Following oral exposure, the highest levels have been detected in the lungs and blood. Animal studies have shown that cyanide does not accumulate in the blood and tissues following chronic oral exposure. Cyanide is transformed to thiocyanate in the body, with a plasma half-life of 20 minutes to one hour. Cyanide metabolites are excreted primarily in the urine, with small amounts excreted through the lungs.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Cyanide is rapidly absorbed (within seconds) following inhalation exposure. Humans retained 58% of hydrogen cyanide in the lungs after inhaling the gas through normal breathing (Landahl and Herrmann 1950).

Quantitative data on the absorption of hydrogen cyanide by inhalation were reported in dogs (Gettler and Baine 1938). During exposure to an unknown concentration of hydrogen cyanide, one dog reportedly absorbed 16.0 mg (1.55 mg/kg); the other dog absorbed 10.1 mg (1.11 mg/kg). These doses were fatal to the dogs in 15 and 10 minutes, respectively. More recent quantitative data were not available.

2.3.1.2 Oral Exposure

Information regarding the rapid lethal effects following oral intake of cyanide in humans indicates that cyanide is rapidly absorbed from the gastrointestinal tract. In a case study, an 80-kg male ingested an estimated 15-25 mg CN^-/kg as potassium cyanide in a suicide attempt (Liebowitz and Schwartz 1948). Based on a concentration of 200 mg hydrogen cyanide/L in the blood 2 hours after ingestion, it was

estimated that the patient had 1.2 g hydrogen cyanide in the blood, with ~2.3 g CN^- in the body, after 2 hours.

Three dogs were given lethal doses of cyanide by gavage. The amount of cyanide absorbed was determined by the difference between the cyanide given and the cyanide left in the stomach and intestines (Gettler and Baine 1938). The dogs died 8,21, and 155 minutes after treatment and had absorbed 17,24, and 72%, respectively, of the dose given. Rats excreted 47% of a dose of radioactivity in the urine during 24 hours following gavage treatment with 2 mg CN^-/kg as radiolabeled potassium cyanide (Farooqui and Ahmed 1982), indicating that at least 53% of the cyanide was absorbed in 24 hours. More detail on the mechanism of absorption is provided in Section 2.4.1.

2.3.1.3 Dermal Exposure

No studies were located regarding quantitative absorption in humans after dermal exposure to cyanide gas or common inorganic salts. Evidence that cyanide can be absorbed through the skin of humans is provided in case reports of toxic effects in humans after accidental dermal contact with cyanide (see Section 2.2.3).

Information regarding dermal absorption of cyanide in animals was provided in studies of guinea pigs and dogs (Walton and Witherspoon 1926). When a small area of the shaved abdomen of guinea pigs was exposed to hydrogen cyanide vapor for 30-60 minutes, signs of cyanide toxicity observed included rapid respiration followed by general twitching of muscles, convulsions, and death. In a similar experiment, shaved and unshaved dogs were placed in a chamber in which their bodies, with the exception of the head and neck, were exposed to hydrogen cyanide vapor. No signs of toxicity were reported after exposure to 4,975 ppm hydrogen cyanide for 180 minutes. Deaths occurred after exposure to 13,400 ppm hydrogen cyanide for 47 minutes and suggested dermal absorption. Further indirect evidence regarding dermal absorption of cyanide as hydrogen cyanide or its salts (Ballantyne 1983a, 1983b, 1988) can be found in Section 2.2.3.

2. HEALTH EFFECTS

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

Once cyanide is absorbed, it is rapidly distributed by the blood throughout the body. Tissue levels of hydrogen cyanide were 0.75, 0.42, 0.41,0.33, and 0.32 mg/100 g of tissue in the lung, heart, blood, kidney, and brain, respectively, in a man who died following inhalation exposure to hydrogen cyanide gas. In one case of death due to cyanide exposure, it was estimated that 30 mg of hydrogen cyanide had been ingested and that 3 hours had elapsed before death (Gettler and Baine 1938). In another case, tissue cyanide levels from a man who died from inhalation of hydrogen cyanide were reported as 0.5 mg per 100 mL of blood and 0.11,0.07, and 0.03 mg/l00 g in the kidney, brain, and liver, respectively. Urinary cyanide levels were reported as 0.2 mg/l00 mL, and 0.03 mg/l00 g were found in the gastric contents (Finck 1969). Following chronic occupational exposure to 0.19-0.75 ppm hydrogen cyanide, 56.0 and 18.3 yg CN-/100 mL were found in the blood of smokers and nonsmokers, respectively (Chandra et al. 1980). The cyanide levels in control groups were 4.8 yg/mL for smokers and 3.2 µg/mL for nonsmokers. In two dogs exposed to unspecified fatal concentrations of hydrogen cyanide, the highest cyanide levels were found in the lungs, blood, and heart (Gettler and Baine 1938). Rats exposed to hydrogen cyanide gas at 356 or 1,180 ppm died within 10 and 5 minutes, respectively (Yamamoto et al. 1982). Samples taken immediately after respiration stopped, showed that the pattern of tissue distribution of cyanide did not vary with the concentration used. In averaging data for both dose groups, tissue concentrations, reported as l.tg/g wet weight (ww), were 4.4 in the lungs, 3.0 in the blood, 2.15 in the liver, 1.4 in the brain, and 0.68 in the spleen. Thus, the highest cyanide concentrations were observed in the lung. Rabbits exposed to hydrogen cyanide at 2,714 ppm for 5 minutes had blood and serum cyanide levels of 170 and 48 µg/dL, and tissue levels (in units of µg/l00 g) of 0 in the liver, 6 in the kidney, 50 in the brain, 62 in the heart, 54 in the lung, and 6 in the spleen (Ballantyne 1983a).

2.3.2.2 Oral Exposure

Small but significant levels of cyanide are present in normal blood plasma at concentrations of 0-14 µg %. (Feldstein and Klendshoj 1954). Vitamin B_{12} contains cyanide, with the source of cyanide attributed to breakdown of cyanogenic foods by bacteria in the gut.

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Cyanide levels in a woman who died 30 minutes after ingesting ≈ 1,325 mg cyanide as sodium cyanide were, in mg %: stomach contents, 3.2; brain, 0.7; urine, 0.5; blood, 0.4; kidney, 0.2; stomach wall, 0.2; and liver, 0.1 (Ansell and Lewis 1970). The mean organ levels of cyanide ion in cases of fatal poisoning in 17-58 cases were, in mg %: stomach contents, 160; spleen, 3.77; blood, 2.39; liver, 1.62; brain, 1.2; kidney, 0.61; and urine, 0.06 (Ansell and Lewis 1970). Brain cyanide levels ranged from 0.06 to 1.37 mg hydrogen cyanide/100 g of tissue in 4 humans who ingested fatal doses of cyanide (Gettler and Baine 1938). Cyanide levels in the livers of 6 humans ranged from 0.22 to 0.91 mg hydrogen cyanide1100 g of tissue. In two cases in which men died from ingestion of unknown quantities of unspecified cyanide salts, cyanide levels were highest in the gastric contents, and next highest in the lungs and blood (Finck 1969).

Combined data from 9 to 10 rats that died 3.3 and 10.3 minutes after gavage doses of 7 or 21 mg CN-/kg as sodium cyanide showed average tissue concentrations of cyanide in l µg/g ww of: liver, 8.9; lung, 5.8; blood, 4.9; spleen, 2.1; and brain, 1.5 (Yamamoto et al. 1982). When 6 rats were treated with 4 mg CN^-/kg as potassium cyanide, signs of central nervous system toxicity were observed (Ahmed and Farooqui 1982), and cyanide levels 1 hour after exposure were 3,380 µg /g in liver, 748 µg /g in brain, and 550 µg/g in kidney. In a study using orally administered radioactively labelled potassium cyanide, the radioactivity detected in whole blood or plasma decreased rapidly within 6 hours. Of the low levels of radioactivity detected in red blood cells, about 94% of the radioactivity recovered was found in the hemolysate; of which 70% was detected in the heme fraction; 14-25% in globin; and only 5-10% in cell membranes (Farooqui and Ahmed 1982). Rabbits treated by gavage with 11.9-20.3 mg CN^-/kg as hydrogen cyanide had blood and serum cyanide levels of 480 and 252 pg/dL respectively, and tissue levels (µg/100 g wet tissue) of 512 in liver, 83 in kidney, 95 in brain, 105 in the heart, 107 in the lung, and 72 in the spleen at the time of death (Ballantyne 1983a).

Cyanide has not been shown to accumulate in the blood and tissues following chronic oral exposure to inorganic cyanides. Following the treatment of groups of 10 male and 10 female rats with hydrogen cyanide in the diet at < 10.4 mg CN^-/kg/day for 2 years, virtually no cyanide was found in plasma or kidneys (Howard and Hanzal 1955). Low levels were found in erythrocytes (mean of 1.9 µg /l00 g). Levels of thiocyanate, the less toxic primary metabolite of cyanide, increased 3.5-fold in plasma, 3.3-fold in erythrocytes, 1.3-fold in liver, and 2.5-fold in kidney.

2.3.2.3 Dermal Exposure

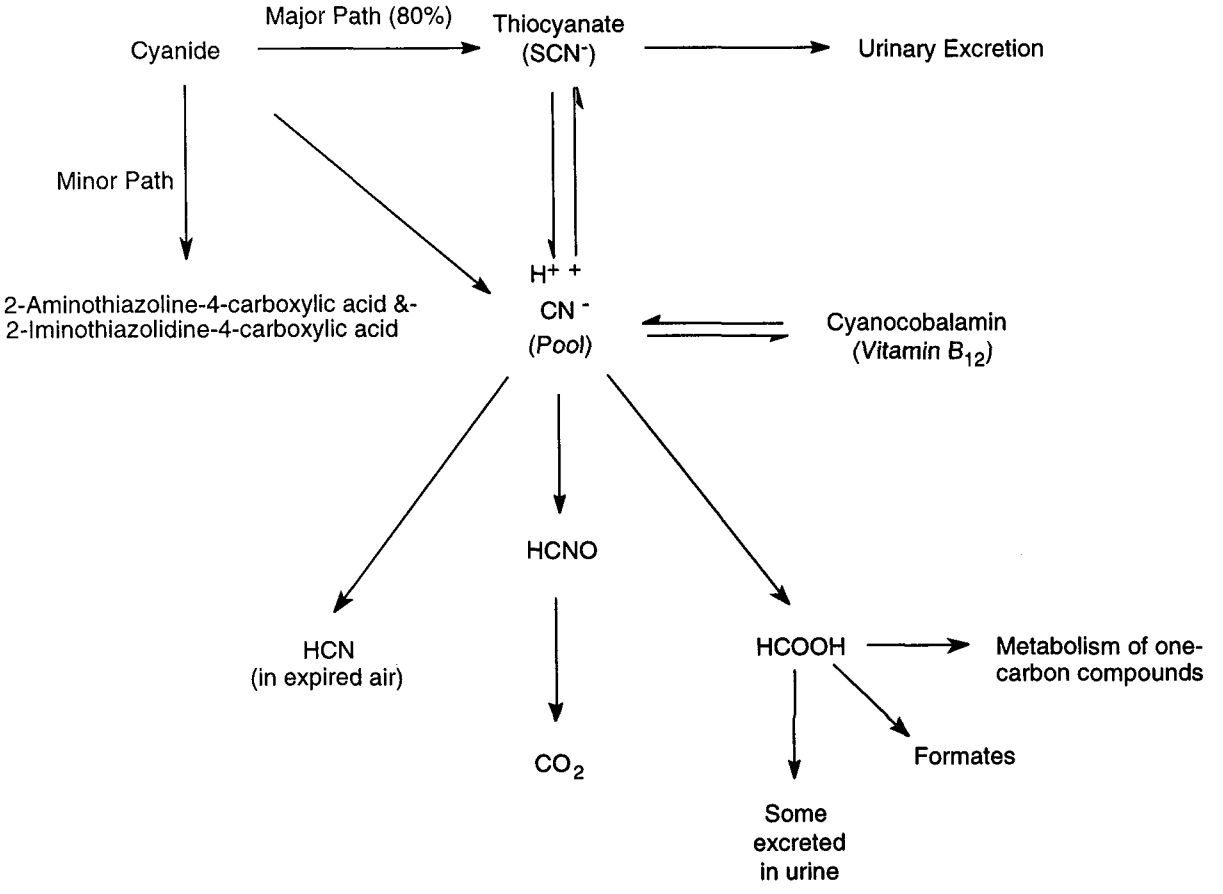
No studies were located regarding distribution in humans after dermal exposure to cyanide.
Six rabbits exposed dermally to 33.75 mg CN^-/kg as hydrogen cyanide had blood and serum cyanide levels of 310 and 144 pg/dL, respectively, and tissue levels µg /100 g) of 26 in liver, 66 in kidney, 97 in brain, 110 in heart, 120 in lungs, and 21 in the spleen (Ballantyne 1983a). Cyanide concentrations were measured immediately after rabbits died, 3-12 minutes after administration of 5.25 mg CN^-/kg as hydrogen cyanide, sodium cyanide, or potassium cyanide to their conjunctival sac (Ballantyne 1983b). Higher cyanide levels were observed in whole blood than in serum in all three groups. However, blood and serum cyanide levels were significantly lower in sodium cyanide and potassium cyanide groups than in the hydrogen cyanide group. Hydrogen cyanide-treated rabbits also had higher concentrations of cyanide in myocardium, lungs, and brain than rabbits from the other two groups. In all groups, the least amount of cyanide was found in the liver and kidney.

2.3.3 Metabolism

Reports of ingestion of cyanides by humans and reports of occupational exposure (see Section 2.5.1) indicate that cyanide is transformed into thiocyanate. A plasma half-life of 20 minutes to 1 hour has been estimated for cyanides in humans after nonlethal exposures (Hartung 1982).

The metabolism of cyanide has been studied in animals. The proposed metabolic pathways shown in Figure 2-3 are (1) the major pathway, conversion to thiocyanate by either rhodanese or 3-mercaptopyruvate sulfur transferase; (2) conversion to 2-aminothiazoline-4-carboxylic acid (Wood and Cooley 1956); (3) incorporation into a 1 -carbon metabolic pool (Boxer and Richards 1952); or (4) combining with hydroxocobalamin to form cyanocobalamin (vitamin B_{12}) (Ansell and Lewis 1970). Thiocyanate has been shown to account for 60-80% of an administered cyanide dose (Blakley and Coop 1949; Wood and Cooley 1956) while 2-aminothiazoline-4-carboxylic acid accounts for about 15% of the dose (Wood and Cooley 1956). The conversion of cyanide to thiocyanate was first demonstrated in 1894. Conversion of cyanide to thiocyanate is enhanced when cyanide poisoning is treated by intravenous administration of a sulfur donor (Smith 1996; Way 1984). The sulfur donor must have a sulfane sulfur, a sulfur bonded to another sulfur (e.g., sodium thiosulfate). During conversion by rhodanese, a sulfur atom is transferred from the donor to the enzyme, forming a persulfide intermediate. The persulfide sulfur is then transferred

Figure 2-3. Basic Processes Involved in the Metabolism of Cyanide



from the enzyme to cyanide, yielding thiocyanate. Thiocyanate is then readily excreted in the urine as the major metabolite. Once thiocyanate is formed, it is not converted back to cyanide.

Radioisotopic studies showed that albumin interacts with the sulfane pool and that the serum albuminsulfane sulfur carrier complex can react with cyanide (Schneider and Westley 1969). Higher hepatic rhodanese and lower serum albumin levels were found in mice fed a protein-free diet for 14 days compared with mice fed a control diet (Rutkowski et al. 1985). Despite the higher rhodanese levels, mortality following an intraperitoneal injection of sodium cyanide was higher in mice fed the protein-free diet both with and without thiosulfate pretreatment. In mice fed the control diet in reduced amounts, serum albumin levels were higher than controls. Mortality in food-deprived mice was also higher compared with controls, but only at high cyanide doses when thiosulfate was also administered. However, the pharmacokinetic studies in dogs suggest that the sulfane sulfur pool may play an important role as the central compartment for cyanide detoxification (Sylvester et al. 1983; Way 1984).

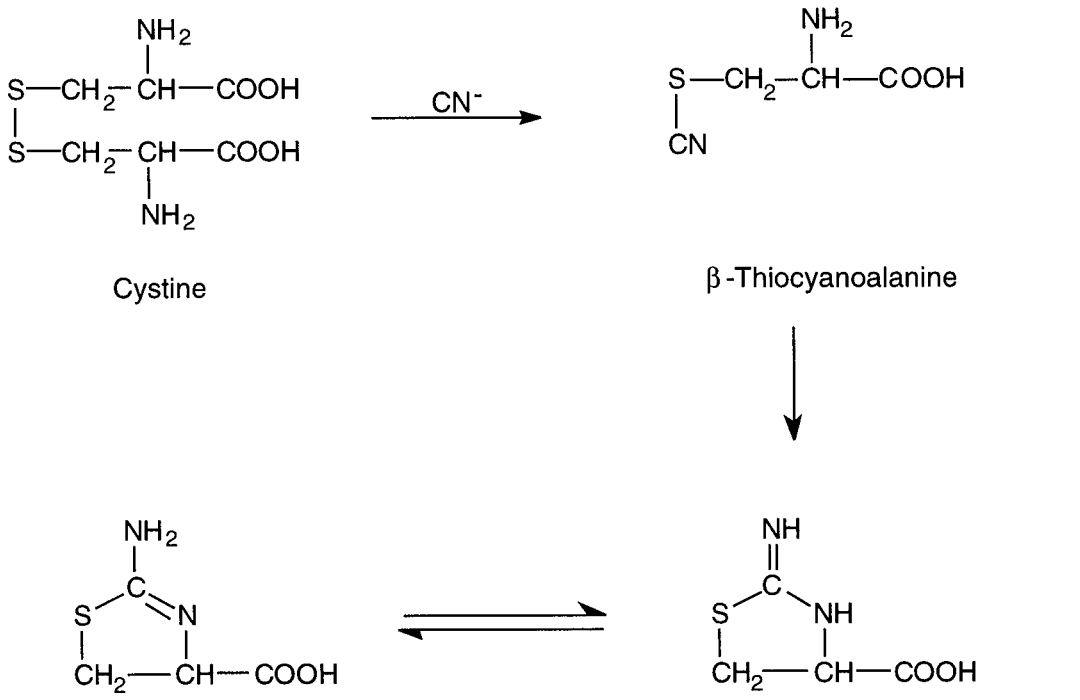
The species and tissue distribution of rhodanese is highly variable (Himwich and Saunders 1948). In dogs, the highest activity of rhodanese was found in the adrenal gland, ≈ 2.5 times greater than the activity in the liver. Monkeys, rabbits, and rats had the highest rhodanese activity in the liver and kidney, with relatively low levels in the adrenals. It should be noted that total rhodanese activity in other species was higher than in dogs, which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Similar low levels of activity of the enzyme were found for the brain, testes, lungs, spleen, and muscle among various species.

In vitro studies with rat tissues indicated that rhodanese activity was ≈ 7 times higher in the nasal mucosa than in the liver (Dahl 1989). Furthermore, kinetic constants for rhodanese in mitochondria were higher in nasal than in liver tissue.

Figure 2-4 illustrates the minor pathway for metabolism of cyanide in mammalian systems in which cyanide chemically combines with the amino acid cystine. This chemical reaction yields cysteine and β-thiocyanoalanine that is further converted to form 2-aminothiazoline-4-carboxylic acid and its tautomer, 2-iminothiazolidiene-4-carboxylic acid.

Reactions of cyanide with the salts or esters of some amino acids (e.g., pyruvate, α-ketoglutarate, oxaloacetate) lead to formation of cyanohydrin intermediates and their incorporation into intermediary metabolism.

Figure 2-4. Minor Path for the Removal of Cyanide from the Body



Cystine

β-Thiocyanoalanine

2-Aminothiazoline-4-carboxylic acid

2-Imino-4-thiazolidine-carboxylic acid

Source: Ansell and Lewis 1970

2. HEALTH EFFECTS

The ability of cyanide to form complexes with some metallic ions such as cobalt is the basis for the reaction with hydroxocobalamin that yields cyanocobalamin. Cyanocobalamin (vitamin B_{12}), which contains cyanide and cobalt, is essential for the health of mammalian organisms.

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Following chronic occupational exposure to 0.19-0.75 ppm hydrogen cyanide, 24-hour urinary levels of thiocyanate were 6.23 (smokers) and 5.4 µg /mL (nonsmokers) in exposed workers as compared with 3.2 (smokers) and 2.15 µg /mL (nonsmokers) in the controls (Chandra et al. 1980). This study demonstrates that tobacco smoking contributes to higher thiocyanate levels excreted in the urine. No studies were located regarding excretion of cyanide in animals after inhalation exposure to cyanide.

2.3.4.2 Oral Exposure

Cyanide metabolites are normally excreted in urine (Vassel et al. 1944) with small amounts eliminated through the lungs. Urinary excretion of thiocyanate was monitored in a man after ingestion of ≈ 3-5 g potassium cyanide (15-25 mg CN^-/kg) (Liebowitz and Schwartz 1948). The results indicated that the patient excreted 237 mg of thiocyanate over a 72-hour period. This quantity was substantially more than the normal average amount of thiocyanate in urine, which varies between 0.85 and 14 mg/24 hours. Thirty-one children who had consumed flour made from insufficiently processed cassava had mean urinary thiocyanate levels of 757 ymol/L, compared with 50 µmol/L in those children who had consumed sufficiently processed cassava (Tylleskar et al. 1992). In another study (Mlingi et al. 1993), mean urinary thiocyanate was 490 µmol/L in a village affected by Konzo disease, and 350 µmol/L in an unaffected village, with the villages being comparable in all other respects.

When rats were given 2 mg CN^-/kg [^{12}C] potassium cyanide, urinary excretion of radioactivity reached 47% of the dose within 24 hours following administration (Farooqui and Ahmed 1982). When [^{14}C] sodium cyanide was injected subcutaneously into rats at a level of 8.3 µmol, no difference in radioactivity eliminated was observed between the group pretreated for 6 weeks with a diet containing 0.7 mg CN^-/kg as potassium cyanide and their matching controls (Okoh 1983). Most of the radioactivity was detected in the urine (89% by 24 hours). Thiocyanate was the major metabolite. About 4% of the radioactivity was expired, mostly as carbon dioxide.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to cyanide.

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 199Os, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substancespecific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-5 shows a conceptualized representation of a PBPK model.

If PBPK models for cyanide exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models were located for cyanide.

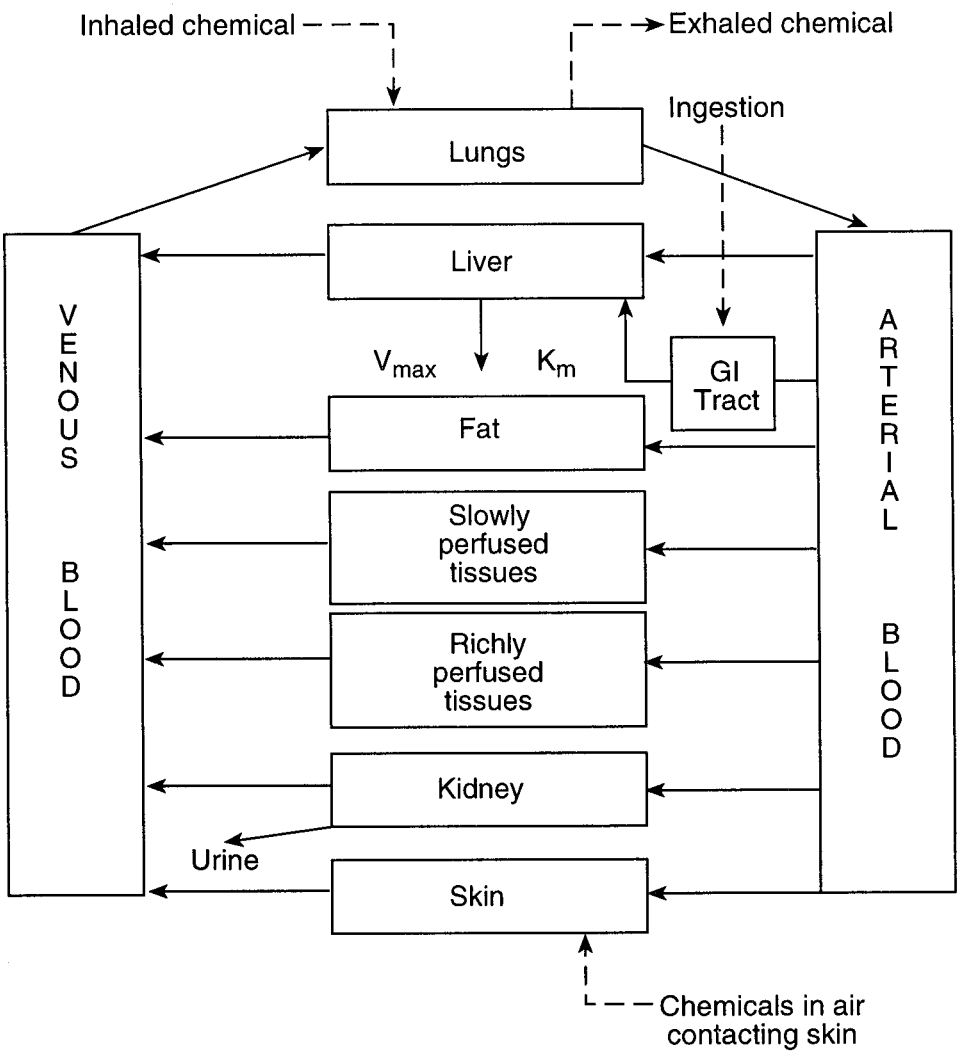
2.4 MECHANISMS OF ACTION

This section presents a brief overview of any known mechanisms of metabolism, absorption, distribution, and excretion including substance reactions or physiological processes that lead to or comprise the mechanism(s) of toxic effect.

2.4.1 Pharmacokinetic Mechanisms

Absorption. Absorption of cyanide across the gastrointestinal mucosa depends on the pH of the gut and the pKa and lipid solubility of the particular cyanide compound. Hydrogen cyanide is a weak acid with a pKa of 9.2 at 25 °C. The acidic environment in the stomach favors the non-ionized form of hydrogen cyanide and facilitates absorption. Information regarding the rapid lethal effects following oral intake of cyanide in humans (Gosselin et al. 1976) indicates that cyanide is rapidly absorbed from the gastrointestinal tract.

Figure 2-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1992

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

2. HEALTH EFFECTS

Hydrogen cyanide is moderately lipid-soluble, which, along with its small size, allows it to rapidly cross mucous membranes, to be taken up instantly after inhalation, and to penetrate the epidermis. In addition, some cyanide compounds, such as potassium cyanide, have a corrosive effect on the skin that can increase the rate of percutaneous absorption (NIOSH 1976). Information regarding dermal absorption in animals and evidence that cyanide can be absorbed through the skin of humans is provided in Sections 2.3.1.3 and 2.2.3, respectively.

Distribution. Cyanide is rapidly distributed by the blood throughout the body. In a study using orally administered radioactively labelled potassium cyanide, radioactivity detected in whole blood or plasma decreased rapidly within 6 hours. Of the low levels of radioactivity detected in the red blood cells, about 94% of the radioactivity recovered was found in the hemolysate; of which 70% was detected in the heme fraction, 14-25% in globin, and only 5-10% in cell membranes (Farooqui and Ahmed 1982). Yamamoto et al. (1982) determined that the pattern of distribution of cyanide did not vary with the concentration used. Ballantyne (1983b) observed higher cyanide levels in whole blood than in serum in rabbits exposed dermally to hydrogen cyanide, potassium cyanide, and sodium cyanide. See Section 2.3.2.1 for specific studies on cyanide tissue distribution.

Cyanide is a reactive chemical substance and has the potential to form a variety of adducts in biological systems. A study of radiolabeled cyanide binding to mouse brain parts revealed that the hypothalamus accumulated more label than cerebral cortex, hippocampus, or cerebellum (Borowitz et al. 1994). Similarly, Baskin et al. (1987) found that the left ventricle of the guinea pig heart contained nearly twice as much as the right ventricle after a brief exposure to cyanide. Binding to certain tissue constituents may be important for decreasing the actions of cyanide and protecting cells from cyanide toxicity (Devlin et al. 1989b).

Storage. Cyanide does not accumulate in blood and tissues following chronic oral exposure. In a study with rats administered hydrogen cyanide in the diet at ≈10.4 mg CN^-/kg/day for 2 years, virtually no cyanide was found in plasma or kidneys (Howard and Hanzal 1955).

Excretion. Cyanide metabolites (of which thiocyanate is the major component) are excreted primarily in urine, with small amounts of the metabolites eliminated through the lungs. When radioactively labeled cyanide is administered, most of the radioactivity is detected in the urine within 24 hours (Farooqui and Ahmed 1982; Okoh 1983). Boxer and Richards (1952) were the first to show that cyanide was oxidized to

CO_2 and in the Okoh (1983) study, about 4% of the radioactivity was expired, mostly as carbon dioxide. See Section 2.3.4 for information on studies examining elimination and excretion.

Effect of Dose and Duration of Exposure on Toxicity. The severity of neurological effects in humans and animals after acute oral exposure to cyanide is dose-related (Chen and Rose 1952; Lasch and El Shawa 1981). Central nervous system effects have been observed following acute-duration exposures (Levine and Stypulkowski 1959a) and chronic-duration exposures (Hertting et al. 1960), via the inhalation and oral routes. Necrosis is the most prevalent central nervous system effect following acute-duration exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963).

Increased duration of exposure to inhaled cyanide in mice resulted in lower LC_{50} values (Higgins et al. 1972; Matijak-Schaper and Alarie 1982). Additionally, cyanide toxicity was influenced by dilution of the gavage dose. Greater dilution resulted in higher mortality for the same total dose (Ferguson 1962).

Tylleskar et al. (1992) studied a population in rural Zaire that was affected with Konzo. Konzo is characterized by symmetric isolated bilateral involvement of upper motor neurons of abrupt onset; the damage is permanent but not progressive. The Konzo patients had serum thiocyanate concentrations below those of the controls. The authors suggest that the combination of high exposure and a decreased conversion rate because of a deficiency in suitable sulfur substrates might explain this difference. Thus, daily exposure and decreased conversion rates may lead to high blood concentrations of cyanide that may lead to upper motor neuron damage. It has been suggested that defects in the metabolic conversion of cyanide to thiocyanate, as well as nutritional deficiencies of protein and vitamin B_{12} play a role in the development of central nervous system disorders such as tropical ataxic neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy.

Route-Dependent Toxicity. A great similarity exists among cyanide-induced effects following inhalation, oral, and dermal exposure. Signs of toxicity in target organs from acute cyanide exposure (primarily central nervous system and heart), and chronic exposure (including central nervous system and thyroid gland), are similar in both humans and animals regardless of route.

2. HEALTH EFFECTS

2.4.2 Mechanisms of Toxicity

Effects of Metabolism on Toxicity. Cyanide (as hydrogen cyanide), originating *in vivo* by dissociation of potassium cyanide, sodium cyanide, and other cyanogenic compounds or arising from catabolism of cyanogenic glycosides, exerts its acute toxic effects by complexing with the ferric iron atom in metalloenzymes, resulting in histotoxic anoxia through inhibition of cytochrome c oxidase (DiPalma 1971; Way 1984), metalloenzymes which function as the terminal oxidase of the inner mitochondrial membrane respiratory chain. A two-step process has been proposed: cyanide as hydrogen cyanide first penetrates a protein crevice of cytochrome c oxidase and binds to the protein (Stannard and Horecker 1948). Hydrogen cyanide then binds to the trivalent iron ion of the enzyme, forming a relatively stable (but reversible) coordination complex. One mole of hydrogen cyanide is bound to one mole of cytochrome c oxidase (Van Buuren et al. 1972). As a result, the enzyme becomes unable to catalyze the reactions in which electrons would be transferred from reduced cytochrome to oxygen. Cellular oxygen utilization is thus impaired, with resultant reduction in or cessation of aerobic metabolism (Rieders 1971; Way 1984). Glucose catabolism then shifts from the aerobic pathway to anaerobic metabolism including the pentose phosphate pathway, resulting in increased blood glucose, pyruvic acid, lactic acid, and nicotinamide adenine dinucleotide (NADPH) levels, and a decrease in the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio (Rieders 197 1; Way 1984). Wilson et al. (1994) suggest that it is the binding of cyanide to oxidized Cu_B in an enzyme containing a single electron that leads to the inhibition of cytochrome c oxidase.

The inhibition of oxygen use by cells (termed histoxic hypoxia) causes oxygen tensions to rise in peripheral tissues (Smith 1996). This results in a decrease in the unloading gradient for oxyhemoglobin; thus, oxyhemoglobin is carried in the venous blood (Rieders 1971). Inhibition of oxygen utilization is thought to occur rapidly after cyanide exposure. Tadic (1992) determined that inhibition of cytochrome c oxidase activity in rat brains was most pronounced between 15 and 20 minutes after administration of sodium cyanide (12 mg/kg or $1.3xLD_{50}$). In addition to binding to cytochrome c oxidase, cyanide also binds to catalase, peroxidase, methemoglobin, hydroxocobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthine oxidase, and succinic dehydrogenase. These reactions may also contribute to the classic signs of cyanide toxicity (Ardelt et al. 1989; DiPalma 1971; Rieders 1971). Information on mechanisms of toxicity in target organs is presented below.

Target Organ Toxicity. The central nervous system is the primary target for cyanide toxicity in humans and animals. Acute inhalation of high concentrations of cyanide provokes a brief central nervous

system stimulation followed by depression, convulsions, coma, and death in humans (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989) and in animals (Haymaker et al. 1952; McNerney and Schrenk 1960; Purser et al. 1984). The effects are probably due to rapid biochemical changes in the brain, such as changes in ion flux, neurotransmitter release, and possibly peroxide formation (Johnson and Isom 1985; Kanthasamy et al. 1991a, 1994; Persson et al. 1985). In both in viva and *in vitro* studies using brain tissue, the sensitivity of mitochondrial cytochrome c oxidase activity to inhibition by cyanide was greater than the inhibition of mitochondrial respiratory activity. Only after cytochrome c oxidase activity was depressed by >50% was a large decrease in respiratory activity detected, suggesting that a large portion of cytochrome c oxidase may serves as a functional reserve. Cyanide poisoning likely involves mechanisms in addition to inhibition of cytochrome c oxidase activity (Pettersen and Cohen 1993). Cyanide is a strong nucleophile with multiple effects including release of secondary neurotransmitters, release of catecholamines from adrenal glands and adrenergic nerves, and it inhibits antioxidant enzymes in the brain (Smith 1996). However, the extremely low concentration of cyanide required to inhibit the oxidase, the rapid interaction of hydrogen cyanide with the enzyme and the key role of cytochrome c oxidase in aerobic metabolism all combine to make cyanide inhibition of the terminal step of electron transport (Chance and Erecinsk 1971; Gibson and Greenwood 1963) the key molecular target in cyanide poisoning.

Inhalation and oral studies in animals have shown that cyanide exposure leads to encephalopathy in both white and gray matter. In particular, damage has been observed in regions such as the deep cerebral white matter, the corpus callosum, hippocampus, corpora striata, pallium, and substantia nigra. White matter may be more sensitive because of its relatively low cytochrome c oxidase content. Rats treated with a single dose of sodium cyanide subcutaneously developed necrotic lesions of the corpus callosum and optic nerve (Lessell 1971). High mortality was observed among exposed animals. These effects have been observed following acute-duration exposures (Levine and Stypulkowski 1959a) and chronic-duration exposures (Hertting et al. 1960). Necrosis is a prevalent central nervous system effect following acute exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963). The mechanism of cyanide-induced demyelination is not completely understood, but the evidence suggests that a direct effect of cyanide on white matter may not be necessary. It has been suggested that local edema affecting the oligodendrocytes and caused by vascular changes triggered by cyanide represent a primary event in demyelination (Bass 1968; Ibrahim et al. 1963). Aiken and Braitman (1989) determined that cyanide has a direct effect on neurons not mediated by its inhibition of metabolism. Consistent with the view that cyanide toxicity is due to the inability of tissue to utilize oxygen is a report that in cyanide-intoxicated rats, arterial pO_2

levels rose, while carbon dioxide levels fell (Brierley et al. 1976). The authors suggested that the low levels of carbon dioxide may have led to vasoconstriction and reduction in brain blood flow; therefore, brain damage may have been due to both histotoxic and anoxic effects. Partial remyelination after cessation of exposure has been reported, but it is apparent that this process, unlike that in the peripheral nervous system, is slow and incomplete (Hirano et al. 1968). The topographic selectivity of cyanideinduced encephalopathy may be related to the depth of acute intoxication and distribution of blood flow, which may result in selected regions of vascular insufficiency (Levine 1969).

Several recent studies have suggested that a disruption in neuronal calcium regulation may be an important factor in the manifestation of cyanide-induced neurotoxic events following acute exposure. The predominance of anaerobic metabolism in a cyanide-poisoned cell decreases the ATP/ADP ratio, or energy charge (Isom et al. 1975), and thus alters energy-dependent processes such as cellular calcium homeostasis (Johnson et al. 1986). Elevated levels of intracellular calcium in a cyanide-exposed, presynaptic squid neuron were observed in an *in vitro* study (Adams et al. 1985). Elevated levels of neuronal calcium may initiate release of neurotransmitters from the presynaptic terminal, which can activate the nervous system (Maduh et al. 1990a). Levels of whole-brain calcium increased when potassium cyanide was administered subcutaneously to mice. These increases were correlated with cyanide-induced tremors (Johnson et al. 1986). Brain injury may be associated with cyanide-induced endogenous glutamate release, mediated by both calcium dependent and independent mechanisms, which in turn produce excitotoxic responses in select brain areas (Pate1 et al. 1991, 1992, 1993). In examining receptor subtypes involved in mediating cyanide-induced toxicity, sodium cyanide-induced cytotoxicity was found to be mediated primarily by activation of the N-Methyl-D Aspartate (excitatory amino acid) receptor. Strum et al. (1993) examined the ability of adenosine to attenuate the excitotoxicity secondary to glutamate receptor activation following potassium cyanide exposure in hippocampal neuronal cell cultures. The authors concluded that neuronal cell death was mediated at least in part by glutamate and that the cell death was attenuated by adenosine via the A_1-specific mechanism. Increases in intracellular calcium have also been associated with cyanide induced effects on vascular smooth muscle and cardiac muscle, possibly inducing cell damage (Allen and Smith 1985; Robinson et al. 1985a). These effects may result from ischemia-induced increases in extracellular potassium, which in turn enhance cellular permeabilities to calcium (Robinson et al. 1985b). Furthermore, changes in cytosolic pH and dysfunction of hydrogen ion handling mechanisms were observed in neuronal cells exposed *in vitro* to cyanide (Maduh et al. 1990b). Pazdemik et al. (1994) reported a global reduction of local cerebral glucose utilization (LCGU) in almost every region of the brain after sublethal exposure to sodium cyanide. These results support the expectation that cyanide

causes a shift from aerobic to anaerobic metabolism, as illustrated by increases in extracellular lactate and pyruvate and in LCGU.

When cyanide blocks oxidative metabolism in mitochondria, cells shift their metabolism and enhanced glucose utilization occurs. One consequence of this altered metabolic pattern is accumulation of nicotinamide adenine dinucleotide (NADH). NADH is a powerful stimulant of calcium mobilization from cell stores through "inositol triphosphate receptors." Elevated calcium damages cells. Increase in cellular NADH, therefore, is an important event in the toxic action of cyanide (Kaplin et al. 1996).

Recent studies have shown that cyanide releases catecholamines from rat pheochromocytoma cells and brain slices (Kanthasamy et al. 1991 b), from isolated bovine adrenal glands (Borowitz et al. 1988), and from adrenals of mice following subcutaneous injection of high doses of potassium cyanide (Kanthasamy et al. 1991b). Thus, it was proposed that the cardiac and peripheral autonomic responses to cyanide are partially mediated by an elevation of plasma catecholamines (Kanthasamy et al. 1991b). Dopamine levels in potassium cyanide-treated animals were significantly decreased in striatum and hippocampus, and somewhat decreased in cerebral cortex of mice (Kanthasamy et al. 1994), while extracellular levels of dopamine and homovanillic acid were increased in the brain of rats treated with sodium cyanide (Cassel et al. 1995). Kiuchi et al. (1992) suggested that suppression of ATP production by sodium cyanide induces an abrupt and remarkable increase in dopamine release from the nerve terminal in the striatum. Kanthasamy et al. (1994) also observed that in striatal and hippocampal tissues, but not in cerebral cortex, malondialdehyde levels increased indicating the occurrence of lipid peroxidation in these brain regions. In addition, reduced numbers of tyrosine hydroxylase (TH) positive cells indicated a loss of dopaminergic neurons (Kanthasamy et al. 1994). Behavioral effects seen in the mice were reversed by administration of I-DOPA (treatment for dopamine-deficiency). Ardelt et al. (1994) also evaluated hydroperoxide generation as a potential mechanism of cyanide neurotoxicity. Increased lipid peroxidation was observed in brain and kidney, but not in liver or heart. It was also determined that calcium plays a critical role in lipid peroxidation in neuronal cells. Subcellular fractionation of brain tissue showed an increase in lipid peroxidation in the microsomal but not mitochondrial fraction. Matsumoto et al. (1993) evaluated the involvement of extracellular calcium in dopamine release from rat striatum resulting from cyanide exposure. A gradual increase in intracellular calcium was observed during incubation of sodium cyanide with striatal slices. The excessive influx of extracellular calcium during sodium cyanide perfusion may contribute to the changes in dopamine levels in striatum and to the observed suppression of dopamine release in response to high potassium stimulation. Release of dopamine was not suppressed by perfusion with a calcium-free solution; thus, additional mechanisms other than the opening of calcium channels

must also be involved in dopamine release by cyanide. Decreased dopamine uptake has been suggested as an explanation for this increase in dopamine, since dopamine uptake is driven by a sodium gradient which is maintained by the Na/K ATPase and could be reduced if ATP is depleted. Cyanide did not affect monamine oxidase or catechol-o-methyl transferase, suggesting that a disturbance in dopamine metabolism did not lead to extracellular dopamine elevation (Matsumoto et al. 1993).

Cassel et al. (1994) examined the *in vitro* effects of sodium cyanide on two forms of monoamine oxidase (MAO), an enzyme important in regulation of biogenic amines in the brain and peripheral tissue. In striatal tissue, cyanide produced a dose-dependent increase in the activity of MAO-A but not MAO-B. Greer and Carter (I 995) investigated the effects of hydrogen cyanide on the neural mechanisms controlling breathing. Cyanide, at concentrations considered lethal *in vivo*, caused a modest depression of the frequency and amplitude of inspiratory rhythmic discharge. The neuronal network underlying respiration continued to function for hours in the presence of very high concentrations of cyanide. The authors hypothesized that the rapid suppression of breathing caused by cyanide *in vivo* is due to changes in neuronal excitability in respiratory centers in the central nervous system, rather than due to cellular metabolism of neurons within respiratory centers.

Results of *in vitro* studies suggest an interaction between calcium ions and cyanide in cardiovascular effects (Allen and Smith 1985; Robinson et al. 1985a). It has been demonstrated that exposure to cyanide in metabolically depleted ferret papillary muscle eventually results in elevated intracellular calcium levels, but only after a substantial contracture develops (Allen and Smith 1985). The authors proposed that intracellular calcium may precipitate cell damage and arrhythmias. The mechanism by which calcium levels are raised was not determined. Franchini and Krieger (1993) produced selective denervation of the aortic and carotid bifurcation areas, and confirmed the carotid body chemoreceptor origin of cardiovascular, respiratory and certain behavioral responses to cyanide in rats. Bradycardia and hyperventilation induced by cyanide are typical responses evoked by carotid body chemoreceptor stimulation (Franchini and Krieger 1993).

The respiratory effects of cyanide include dyspnea, asphyxia, and a decrease in respiratory rate (Blanc et al. 1985; Matijak-Schaper and Alarie 1982: McNerney and Schrenk 1960). A recent study (Bhattacharya et al. 1994) demonstrated increased air flow, transthoracic pressure, and tidal volume accompanied by a significant decrease in pulmonary phospholipids following inhalation of hydrogen cyanide in rats. This study also showed that hydrogen cyanide exhibited a direct effect on pulmonary cells in rats.

2. HEALTH EFFECTS

Cyanide-induced effects on the thyroid gland are particularly important in chronic cyanide exposures and are discussed in several studies. Thiocyanate markedly inhibits accumulation of iodine by the thyroid gland, thus decreasing the ability of the gland to maintain a concentration of iodine above that of blood (VanderLaan and Bissell 1946). In addition, thiocyanate may inhibit the iodination process, thus interfering with the binding of glandular iodine and reducing the formation of thyroxine (Et-mans et al. 1972). Changes in thyroid chemistry reported in individuals chronically exposed to cyanide have not been accompanied by manifestations of hypothyroidism. Fukayama et al. (1992) studied the antithyroid action of thiocyanate in a culture system of thyroid follicles. Thiocyanate concentrations equivalent to serum levels in smokers showed three independent antithyroid actions, including inhibition of iodide transport, inhibition of binding of iodide in the thyroid, and increased iodide efflux. The discrepancy in the potency of the antithyroid activity of thiocyanate *in vivo* and *in vitro* appears to be due to the presence of iodide and pseudohalogens known to alter the effect of thiocyanate on the thyroid (Van Middlesworth 1986).

Persons with a metabolic disturbance in the conversion of cyanide to thiocyanate may be at greater risk from the toxic effect of cyanide. A defect in the rhodanese system and vitamin B l2 deficiency have been noted in persons with tobacco amblyopia and Leber's hereditary optic atrophy exposed to tobacco smoke which contains cyanide (Wilson 1983). Iodine deficiency, along with excess chronic exposure to cyanide, may in certain cases be involved in the etiology of such thyroid disorders as goiter and cretinism (Delange and Ermans 1971; Ermans et al. 1972). Also, protein deficiencies and vitamin B,, and riboflavin, and other deficiencies may subject people who eat foods high in cyanogenic glycosides to increased risk of neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969). Patients with motor neuron disease (amyotrophic lateral sclerosis) possess a disorder in cyanide metabolism that may result in higher susceptibility to cyanide (Kato et al. 1985).

Carcinogenesis. No studies were located regarding carcinogenic effects of cyanide exposure in humans or animals following any route of exposure. Therefore, no mechanism of carcinogenesis can be discussed.

2.4.3 Animal-to-Human Extrapolations

Biological effects of cyanide in humans have been demonstrated (Smith 1996; Wexler et al. 1947). However, no studies directly comparing the cytotoxicity of similar animal and human cells were available. However, a difference in species susceptibility to cyanide poisoning was indicated by slightly lower lethal concentrations in rabbits compared to rats (Ballantyne 1983a). Additionally, mortality varied depending

on the cyanide compound used. In the Ballantyne (1983a) study, dermal application resulted in cyanide levels in blood and serum that were lower after topical sodium cyanide and potassium cyanide exposure than from hydrogen cyanide; however, oral exposure in rabbits produced an LD_{50} of 2.3-2.7 mg CN^-/kg/day, regardless of whether the source was hydrocyanic acid, sodium cyanide, or potassium cyanide (Ballantyne 1983a).

Species and tissue distribution of rhodanese, an enzyme important in metabolizing cyanide, is highly variable (Himwich and Saunder 1948). In dogs, the highest activity of rhodanese was found in the adrenal gland, ≈ 2.5 times greater than the activity in the liver. Monkeys, rabbits, and rats had the highest rhodanese activity in liver and kidney, with relatively low levels in adrenals. It should be noted that total rhodanese activity in other species was higher than in dogs, which is consistent with the greater susceptibility of dogs to the acute effects of cyanide. Thus, dogs may not be a good model from which to extrapolate the toxicity of cyanide to humans. Similar activities of the enzyme among the species were found for the brain, testes, lungs, spleen, and muscle.

2.5 RELEVANCE TO PUBLIC HEALTH

Overview

Data are available regarding health effects in humans and animals after inhalation, oral, and dermal exposure to cyanide. Cyanide is a highly toxic chemical that can produce death in humans and animals rapidly. This characteristic has long been recognized and, therefore, cyanide has often been used with suicidal and homicidal intent, and as a chemical warfare agent. Of the cyanide compounds, hydrogen cyanide, sodium cyanide, and potassium cyanide are the most common ones in the environment, with gaseous hydrogen cyanide being present in air. Cyanide can be formed during some chemical processes used in industry (for further information see Chapter 4). Thiocyanate is a metabolite of cyanide formed in the body from exposure to cyanide compounds. Dietary sources of cyanide include plants that contain cyanogenic glycosides such as cassava root (tapioca), lima beans, soy, spinach, and certain fruit pits and juices. However, in the United States, cyanide exposure from dietary sources is usually not of concern since the amount of cyanide contained in these sources is very low.

Sufficient concentrations of cyanide cause histotoxic hypoxia in the organism. The toxicity is due to the inability of the tissues to use oxygen. Due to this effect, oxygen tension is usually high in victims of cyanide poisoning. The primary target organs for acute cyanide toxicity are the central nervous system

and the heart. Signs of toxicity in acute cyanide poisoning are tachypnea, incoordination of movements, cardiac irregularities, convulsions, coma, respiratory failure, and death. These effects are common to both humans and animals. Furthermore, a great similarity exists among cyanide-induced effects following inhalation, oral, and dermal exposure. The target organs of chronic cyanide toxicity are the central nervous system, reproductive system, and thyroid gland. No definitive studies were located regarding developmental and reproductive effects in humans after exposure to cyanide or ingestion of foods containing cyanogenic plant material. However, oral studies in animals indicate possible developmental toxicity. No studies were located regarding carcinogenic effects of cyanide.

Minimal Risk Levels for Cyanide

Inhalation MRLs

No acute-, intermediate-, or chronic-duration inhalation MRLs were derived for cyanide because of the limitations associated with the available studies. Many of the animal and human studies used lethality, or serious effects, such as coma, as the end point. Two epidemiological studies are available; however, one study lacked good exposure data, and the other study involved occupational exposure in the electroplating industry where exposure to other chemicals may have occurred.

Oral MRLs

An acute oral MRL was not derived for cyanide because most of the available studies reported lethality as an end point, and there is a lack of information regarding acute systemic effects in animals.

- An MRL of 0.05 mg/kg/day has been derived for intermediate-duration (15-364 days) oral exposure to cyanide.

This MRL was derived from a NOAEL of 4.5 mg/kg/day in a study in which groups of 10 male and 10 female rats were given 0,0.2,0.5, 1.4 (males), 1.7 (females), 4.5 (males), 4.9 (females), or 12.5 mg/kg/day cyanide in the drinking water for 13 weeks, as sodium cyanide (NTP 1993). At the end of the study, the animals were evaluated for histopathology, clinical chemistry, urine chemistry, and reproductive toxicity. A number of reproductive effects, such as decreases in left epididymis weight, left cauda epididymis weight, left testis weight, spermatid heads, and spermatid counts were observed at 12.5 mg/kg/day. At 1.4 and 4.5 mg/kg/day, significantly decreased weight of the left cauda epididymis

and spermatozoa motility were observed; however, these effects alone were not considered to be adverse. For females, more time was spent in the proestrus and diestrus stages, and less time in estrus and metestrus stages in the 4.9 and 12.7 mg/kg/day dose groups; however, this was considered to be a minimal effect. The 12.5 mg/kg/day dose was identified as the LOAEL, based on all the reproductive effects observed in male rats, and the 4.5 mg/kg/day dose was identified as the NOAEL. This NOAEL was used with an uncertainty factor of 100 (10 for extrapolation of animals to humans and 10 for human variability) to derive an MRL. It is important to note that this MRL was based on a study using sodium cyanide, which is a soluble form of cyanide. In addition, a LOAEL of 1.04 mg/kg/day based on systemic and reproductive effects in dogs was identified (Kamalu 1993). However, this study was not used to derive the intermediate oral MRL because dogs are not a good model for human toxicity because dogs have very low levels of rhodenase, an enzyme which is used to detoxify cyanide.

A chronic oral MRL was not derived because of the limitations of the available studies. Human studies that described dietary exposure to cyanide through consumption of cassava lacked quantitative exposure information. The one available chronic oral study in rats found no treatment related effects (Howard and Hanzel 1955).

Death. The signs of cyanide toxicity at concentrations leading to death in humans are well described. Intoxication at ≥ 2,000 ppm hydrogen cyanide is characterized by a brief sensation of dryness and burning in the throat due to local irritation, a suffusing warmth, and a hunger for air (Rieders 1971). Hyperpnea, and sometimes a brief outcry, follows the first breath. In less than one minute, apnea, a few gasps, collapse, and convulsions occur. Cardiovascular failure may also occur, although the heart may continue to beat for 3-4 minutes after the last breath. Reported signs include a rose-colored hue of the skin and a bitter almond-like odor on the breath. The total absorbed dose of hydrogen cyanide in such rapid deaths can be as low as 0.7 mg/kg. Similar signs were reported following ingestion of high doses of cyanide salts. Within a few minutes after swallowing the toxicant, the victim collapses, frequently with a scream (Gettler and St. George 1934). Dyspnea, convulsions, and death from asphyxia follow. Dermal exposure to cyanide results in comparable effects. Based on case report studies, LC_{50} values for humans were estimated for inhalation (McNamara 1976, as cited in Ballantyne 1987), oral (EPA 1987a), and dermal (Rieders 1971) routes as 524 ppm, 1.52 mg/kg, and 100 mg/kg, respectively.

In general, signs of toxicity preceding death are the same in humans and animals. Dyspnea, convulsions, and asphyxiation occur in animals following all routes of exposure to cyanide. LC_{50} values were provided for inhalation of hydrogen cyanide in rats (Ballantyne 1983a; Higgins et al. 1972), mice (Higgins et al.

1972; Matijak-Schaper and Alarie 1982), and rabbits (Ballantyne 1983a). Lethal concentrations were also reported in dogs (Haymaker et al. 1952; Valade 1952). Lower cyanide concentrations required longer periods of exposure to produce death. The difference in species susceptibility to cyanide poisoning was indicated by lower lethal concentrations in rabbits compared with rats.

Following oral exposure in animals, LD_{50} values were calculated for rats dosed with cyanide as sodium cyanide (Ballantyne 1988; Smyth et al. 1969) and in rabbits treated with cyanide as hydrogen cyanide, sodium cyanide, and potassium cyanide (Ballantyne 1983a). However, the LD_{50} value from the Ballantyne (1988) study is not considered reliable since the animals were starved, and thus physiologically compromised. For oral exposure, the molar lethal toxicities of hydrogen cyanide, sodium cyanide, and potassium cyanide are similar. Rabbits appeared to be more susceptible to the lethal toxicity of these three compounds than were rats (Ballantyne 1988). Cyanide toxicity was influenced by dilution of gavage doses. The higher the dilution, the higher the mortality for the same total dose.

Deaths can occur after dermal exposure to hydrogen cyanide, sodium cyanide, or potassium cyanide (Ballantyne 1983a). The lowest LD_{50} indicating the highest toxicity, was calculated for cyanide applied to the skin in the form of hydrogen cyanide. Potassium cyanide was the least toxic compound. A similar pattern in cyanide toxicity was observed among these three compounds when applied into the inferior conjunctival sac of rabbits (Ballantyne 1983a, 1983b). Dermal absorption and consequent mortality were also observed in guinea pigs (Fairley et al. 1934; Walton and Witherspoon 1926) and in dogs (Walton and Witherspoon 1926) following unspecified doses of hydrogen cyanide. Cyanide absorption and, therefore, toxicity differed in rabbits with dry intact, moist, or abraded skin (Ballantyne 1988), as expected. The lowest LD_{50} for cyanide given as sodium cyanide was calculated for rabbits with abraded skin.

Cyanide can inhibit enzymatic activity by binding to the metallic cofactor in metalloenzymes. Cytochrome c oxidase (an enzyme in the mitochondrial respiratory chain) is sensitive to cyanide action (Way 1984). Due to its inhibition, oxygen cannot be utilized, histotoxic hypoxia develops, and this can lead to deaths of humans and animals (see Section 2.3.3).

The inhibition of oxygen use by cells causes oxygen tensions to rise in peripheral tissues; this results in a decrease in the unloading gradient for oxyhemoglobin. Thus, oxyhemoglobin is carried in the venous blood (Rieders 1971). Inhibition of oxygen utilization is thought to occur rapidly after cyanide exposure. Inhibition of cytochrome G oxidase activity peaked 3-10 minutes following the intraperitoneal administration of potassium cyanide to mice, rats, and gerbils (Schubert and Brill 1968).

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In addition to binding to cytochrome c oxidase, cyanide inhibits catalase, peroxidase, methemoglobin, hydroxocobalamin, phosphatase, tyrosinase, ascorbic acid oxidase, xanthine oxidase, and succinic dehydrogenase activities. These reactions may make contributions to the signs of cyanide toxicity (Ardelt et al. 1989; Rieders 1971). Signs of cyanide intoxication include an initial hyperpnea followed by dyspnea and then convulsions (Rieders 1971; Way 1984). These effects are due to initial stimulation of carotid and aortic bodies and effects on the central nervous system. Death is caused by respiratory collapse resulting from central nervous system toxicity.

The inorganic cyanides and their cyanohydrins are highly toxic chemicals that should be handled only by properly trained personnel, with appropriate protective equipment, using extreme caution. Death can result from exposure by all routes that humans are likely to experience, including transocular. Although cyanides are among the most acutely toxic of all industrial chemicals, they are produced in large quantities, and are used in many applications; however, they have caused few serious accidents or deaths (Hartung 1982). This appears to be due to the fact that it is common knowledge that the cyanides are very toxic materials that need to be treated with due caution.

Systemic Effects

Respiratory Effects. Respiratory effects commonly occur after inorganic cyanide poisoning by any route of exposure. Following inhalation, the first breath of a lethal concentration of hydrogen cyanide causes hyperpnea (Rieders 1971). The victims experience shortness of breath that may be rapidly (>l minute) followed by apnea. Dyspnea was reported in patients who survived acute inhalation exposure to cyanide (Chen and Rose 1952; Peden et al. 1986; Potter 1950). Similarly, dyspnea was observed in humans following acute oral exposure to cyanide as sodium cyanide (Grandas et al. 1989), as potassium cyanide (Goodhart 1994; Liebowitz and Schwartz 1948; Saincher et al. 1994), or as cyanogenic glycosides in apricot pits (Lasch and El Shawa 1981). Likewise, dyspnea occurred following dermal exposure to cyanide as copper cyanide (Dodds and McKnight 1985) and potassium cyanide (Trapp 1970) in occupational accidents. l&mans acutely exposed to cyanogen experienced nasal irritation (McNerney and Schrenk 1960).

Various symptoms indicating respiratory effects were reported in humans exposed to hydrogen cyanide or its salts in occupational settings. Upper respiratory irritation, cough, altered sense of smell, nasal congestion, epistaxis, hemoptysis, and dyspnea were among the clinical signs of cyanide toxicity (Blanc et al. 1985; Chandra et al. 1980; El Ghawabi et al. 1975). The severity of these effects correlated with

cyanide levels in workplace air. It must be pointed out, however, that in occupational settings such as electroplating operations or gold recovery, exposure to other chemicals also occurs.

Exposure to inorganic cyanide, its salts, or cyanohydrins by any route produces similar respiratory effects in animals.

Cardiovascular Effects. Hypotension was the main effect reported in patients after acute inhalation exposure to hydrogen cyanide (Chen and Rose 1952; Peden et al. 1986), as well as after oral exposure to potassium cyanide (Liebowitz and Schwartz 1948) or after ingestion of cyanogenic glycosides in apricot pits (Lasch and El Shawa 198 1). Palpitations were recorded in men exposed dermally to hydrogen cyanide (Drinker 1932). Peripheral vasoconstriction and gross plasma extravasation were found in a man whose whole body was exposed to liquid copper cyanide in a cistern (Dodds and McKnight 1985). In many of these cases, the effects reported may reflect an indirect action mediated by the nervous system. Most individuals experienced marked sinus irregularities and a slowing of heart rate immediately after an intravenous injection of cyanide as sodium cyanide (Wexler et al. 1947). Workers exposed to cyanide during electroplating and silver-reclaiming jobs complained of precordial pains (Blanc et al. 1985; El Ghawabi et al. 1975). During electroplating operations, however, exposure to other chemicals such as cleaners and cutting oils also occurs.

Acute inhalation of hydrogen cyanide resulted in bradycardia, arrhythmia, and T-wave abnormalities (Purser et al. 1984), and increased cardiac-specific creatinine phosphokinase activity (O'Flaherty and Thomas 1982) in monkeys. Isolated strips of aorta from rabbits, dogs, and ferrets were used to determine the effects of cyanide on vascular smooth muscle (Robinson et al. 1985b). Cyanide caused small contractions in the isolated rabbit aorta at low cyanide concentrations; at higher cyanide concentrations, relaxation occurred. It was found that chlorpromazine or 4,4'-diisothiocyano-2, 2'-stilbene disulfonic acid (DIDS) reduced the contractions (Robinson et al. 1985a).

Results of *in vitro* studies suggest that both calcium ions and cyanide are involved in cardiovascular effects. It has been demonstrated that exposure to cyanide in a metabolically depleted ferret papillary muscle eventually results in elevated intracellular calcium levels, but only after a substantial contracture develops (Allen and Smith 1985). The authors proposed that intracellular calcium may precipitate cell damage and arrhythmias. The mechanism by which calcium levels are raised was not determined.

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Gastrointestinal Effects. Information regarding gastrointestinal effects after inhalation and dermal exposure to cyanide is limited. Nausea and vomiting were reported in workers exposed to cyanide (Blanc et al. 1985; El Ghawabi et al. 1975). Similarly, exposure to hydrogen cyanide caused vomiting in dogs (Valade 1952). The only information on dermal exposure was provided in a study with guinea pigs (Fairley et al. 1934). Exposure to hydrogen cyanide produced submucous hemorrhages in the stomach.

Following oral exposure, the recorded effects included vomiting in patients after acute exposure to cyanogenic glycosides in apricot pits (Lasch and El Shawa 1981) and in a man who ingested 7.6 mg CN-/kg in a suicide attempt (Goodhart 1994), gastrointestinal spasms after exposure to cyanide in the form of potassium cyanide (Thomas and Brooks 1970), and gastric necrosis after ingestion of sodium cyanide (Grandas et al. 1989). Furthermore, frequent vomiting was observed in pigs orally exposed to low doses of cyanide as potassium cyanide; however, the animals were experimentally compromised as they were starved (Jackson 1988).

Gastrointestinal effects can be caused by central nervous system stimulation (nausea) or by direct contact (necrosis) with cyanide salts.

Hematological Effects. No pathological changes were found during hematological examinations of an individual following ingestion of 15 mg CN^-/kg as potassium cyanide (Liebowitz and Schwartz 1948). However, increased hemoglobin and lymphocyte counts were found in workers occupationally exposed to 6.4-10.4 ppm cyanide (El Ghawabi et al. 1975). It is possible, however, that chemicals other than cyanide may have contributed to the effects observed in occupationally exposed subjects. In another study (Kumar et al. 1992), an increase in neutrophil values, an increase in erythrocyte sedimentation rate, and a decrease in hemoglobin levels were noted in male workers exposed to unspecified concentrations of cyanide during case hardening and electroplating.

Increases in the mean corpuscular volume of erythrocytes and of hemoglobin concentration suggested hematological effects in rats after exposure to potassium silver cyanide for 90 days (Gerhart 1987b). Decreased hematocrit, erythrocyte count, and hemoglobin concentration were found in rats treated with copper cyanide by gavage during intermediate-duration exposure; however, because of the known hematotoxic properties of copper, these effects could be attributed mainly to copper (Gerhart 1987a). Minimal changes were observed in hematology in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks, and the authors did not consider them to be treatment related (NTP 1993).

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Musculoskeletal Effects. Convulsions are typical symptoms of cyanide poisoning after inhalation (Rieders 1971), oral (Gettler and St. George 1934; Haymaker et al. 1952), or dermal exposure (Ballantyne 1988; Fairley et al. 1934; Walton and Witherspoon 1926). The convulsions indicate involvement of the central nervous system. Furthermore, muscular rigidity was reported after acute inhalation (Haymaker et al. 1952) and oral (Grandas et al. 1989; Saincher et al. 1994) exposure to high levels of cyanide. Skeletal muscle participates significantly in cyanide biotransformation *in vitro* (Devlin et al. 1989a). In muscles sectioned longitudinally, points of rhodanese staining were associated with mitochondria within the fiber. Cyanide clearance in isolated hind limbs of rats was only 1.5 times lower than in the liver (Devlin et al. 1989b). Despite the presence of cyanide in muscles, muscular effects observed in cyanide poisoning victims may in part reflect cyanide toxicity to the central nervous system.

Hepatic Effects. No studies were located regarding hepatic effects in humans after exposure to cyanide by the oral and dermal routes. An increase in serum alkaline phosphatase was noted in workers exposed to unspecified levels of cyanide; however, serum bilirubin was found to be within the normal range in workers exposed to unspecified levels of cyanide (Kumar et al. 1992). Limited information was obtained in animals. Increased bilirubin, alkaline phosphatase, SGOT and SGPT levels, necrosis, and decreased globulin levels were found in the blood of male rats that were dosed with cyanide as copper cyanide. However, these effects were probably mainly due to the toxicity of copper (Gerhart 1987a). Changes in absolute and relative liver weights were observed in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Periportal vacuolation and congestion were observed in the liver of dogs fed cassava, while no hepatic effects were observed in dogs fed rice with sodium cyanide added (Kamalu 1993). No hepatic effects were found in rats gavaged with potassium silver cyanide for the same time period (Gerhart 1987b) or in rats fed for 2 years with a diet fumigated with hydrogen cyanide (Howard and Hanzal 1955). Furthermore, no effects were seen in rats and monkeys following 6 months of inhalation exposure to 11 ppm cyanogen (6 hours a day, 5 days a week) (Lewis et al. 1984).

In vitro studies indicated that cyanide biotransformation in the liver is high because of the high rhodanese activity in the organ (Devlin et al. 1989a). Cyanide extraction ratios and rates of thiosulfate generation were established in isolated rat livers (Devlin et al. 1989b). Cyanide clearance was ≈ 1.5 times greater in liver (calculated for the total mass) as in skeletal muscle. Adding sodium thiosulfate to the system quickly increased the conversion of cyanide to thiocyanate. Interspecies differences in liver rhodanese activity were reported in animals (Drawbaugh and Marrs 1987). The activity was highest in rats, hamsters, and guinea pigs, followed by rabbits, and lowest in marmosets and dogs. This variability can explain

interspecies differences in sensitivity to cyanide toxicity demonstrated by different LC_{50} values. It is evident that the liver plays an important role in cyanide toxicokinetics and it can be anticipated that, following rhodanese inactivation, harmful effects to liver tissue may be expected.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to cyanide. Case reports cited transitory albuminuria in a man ingesting 15 mg CN^-/kg as potassium cyanide (Liebowitz and Schwartz 1948) and transitory oliguria in a man who accidentally fell into a cistern of copper cyanide (Dodds and McKnight 1985). Few studies cited renal effects in animals following oral exposure. Decreased kidney weight was observed in rats exposed to copper cyanide (Gerhart 1987a) and increased blood urea nitrogen was found in rats exposed to potassium silver cyanide (Gerhart 1987b) in the intermediate-duration experiments. Histopathological changes in glomerular cells were reported in pigs fed cassava roots for 110 days (Tewe and Maner 1981b) and in epithelial tubular cells in dogs exposed to sodium cyanide for 14.5 months (Hertting et al. 1960). Changes in absolute and relative kidney weight were observed in rats and mice exposed to sodium cyanide in the drinking water for 13 weeks, but they were minor and sporadic, and the authors did not consider them to be treatment related (NTP 1993). Vacuolation, swelling, and proximal tubular damage with desquamation of the epithelium and casts were observed in the kidneys of dogs fed cassava, while increased urinary protein, casts, and some desquamation, but no damage to the proximal tubules, were observed in dogs fed rice with sodium cyanide added (Kamalu 1993). However, no kidney effects were observed in rats after chronic oral exposure to hydrogen cyanide (Howard and Hanzal 1955) and in rats and monkeys after intermediate duration inhalation exposure to cyanogen (Lewis et al. 1984). Interspecies differences in rhodanese activity in kidneys were found in several species; the differences were similar to those observed for liver rhodanese activity (Drawbaugh and Marrs 1987). There is no conclusive evidence to support a nephrotoxic action of cyanide.

Endocrine Effects. Thiocyanate is goitrogenic in animals and humans (VanderLaan and Bissell 1946). Although within normal limits, statistically significant increased levels of TSH found in workers exposed to cyanide in a silver-reclaiming facility suggested thyroid effects (Blanc et al. 1985). Furthermore, increased radioactive iodine uptake and enlarged thyroid glands were seen in workers exposed to cyanide during electroplating (El Ghawabi et al. 1975). Exposure to other chemicals such as cleaners and cutting oils also occurs during electroplating operations. High incidences of endemic goiter (Delange and Ermans 1971) and a decreased uptake of radioiodine (Cliff et al. 1986; Delange and Ermans 1971) were associated with chronic oral exposure to cyanogenic glycosides in cassava meals. Similar effects were observed in animals. Significant increases in relative thyroid weight were seen in rats that were exposed orally to

potassium cyanide for an intermediate-duration period (Philbrick et al. 1979). In addition, thyroid gland hypofunction was reported in pigs treated with cassava (Tewe and Maner 198 1 b) or with potassium cyanide (Jackson 1988) during intermediate-duration exposure.

Mechanisms of cyanide-induced effects on the thyroid gland are discussed in several studies. Thiocyanate markedly inhibits accumulation of iodine by the thyroid gland, thus decreasing the ability of the gland to maintain a concentration of iodine above that of blood (VanderLaan and Bissell 1946). In addition, thiocyanate may inhibit the iodination process, thus interfering with the organic binding of glandular iodine and reducing the formation of thyroxine (Ermans et al. 1972). Changes in thyroid chemistry reported in individuals exposed to cyanide have not been accompanied by manifestations of hypothyroidism.

No studies were located on the effects of cyanide on the adrenal gland in humans. However, effects on the adrenal gland, including swelling, hemorrhage, and fibrosis, were observed in dogs fed cassava, as well as in dogs fed rice with sodium cyanide added (Kamalu 1993).

DermalEffects. Rashes developed in ≈ 42% of exposed workers in a study of cyanide in workers (Blanc et al. 1985). No dermal lesions were observed in rabbits exposed dermally to cyanogen (McNerney and Schrenk 1960) and vascular congestion was reported in guinea pigs exposed to hydrogen cyanide (Fairley et al. 1934). Following oral exposure in animals, discolored inguinal fur was observed in rats exposed to copper cyanide (Gerhart 1987a) and potassium silver cyanide (Gerhart 1987b) for an intermediate-duration period.

Ocular Effects. Acute exposure to cyanogen gas produced eye irritation in volunteers (McNemey and Schrenk 1960). Similarly, chronic exposure to cyanide in the working environment caused eye irritation in exposed individuals (Blanc et al. 1985). In addition, exposure to potassium silver cyanide caused ocular opacity in exposed animals, but cornea1 opacity is also a sign of excessive exposure to soluble silver salts alone. However, when cyanide was applied to a rabbit's eye, keratitis developed regardless of the chemical form of cyanide used (Ballantyne 1983b).

Body Weight Effects. Decreased body weight was reported in workers occupationally exposed to hydrogen cyanide (Blanc et al. 1985). Weight loss was one of several effects in this particular group of workers who were in poor health due to chronic cyanide exposure, but other chemicals such as cleaners and cutting oils may have contributed to this effect. Decreased weight was recorded in rats after inhalation

exposure to cyanogen for 6 months (Lewis et al. 1984), and decreased weight gain was found in male rats after intermediate-duration oral exposure to copper cyanide (Gerhart 1987a) and potassium silver cyanide (Gerhart 1987b). The changes in body weight are associated with cyanide toxicity. A dose-dependency was observed in some experiments (Gerhart 1987a). A slight decrease in body weight gain was observed in male rats exposed to sodium cyanide in the drinking water for 13 weeks, but no decrease was seen in female rats or mice of either sex (NTP 1993). In all cases cited above, the effects on body weight were seen only in male animals. No body weight effects were observed in female rats (Gerhart 1987a, 1987b; NTP 1993) or female pigs (Tewe and Maner 1981a) exposed orally for an intermediate-duration period. Therefore, male animals appear to be more susceptible to these effects.

Immunological and Lymphoreticular Effects. No studies were located regarding immunological/lumphoreticular effects in humans or animals after cyanide exposure by any route. Therefore, the potential for cyanide to cause immunological/lymphoreticular effects in humans cannot be assessed.

Neurological Effects. The central nervous system is the primary target for cyanide toxicity in humans and animals. Acute-duration inhalation of high concentrations of cyanide provokes a brief central nervous system stimulation followed by depression, convulsions, coma, and death in humans (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989) and in animals (Haymaker et al. 1952; McNerney and Schrenk 1960; Purser et al. 1984; Valade 1952). The effects are probably due to rapid biochemical changes in the brain, such as changes in ion flux, neurotransmitter release, and possibly peroxide formation (Johnson and Isom 1987; Kanthasamy et al. 1991 a; Persson et al. 1985).

Chronic exposure to lower cyanide concentrations in occupational settings causes a variety of symptoms from fatigue, dizziness, headaches (Blanc et al. 1985; Chandra et al. 1988; El Ghawabi et al. 1975) to ringing in the ears, paresthesias of extremities, and syncopes (Blanc et al. 1985), or even hemiparesis and hemianopia (Sandberg 1967). In addition, behavioral changes were reported following prolonged cyanide exposure in humans (Chandra et al. 1988) and in animals (Lewis et al. 1984), and a loss of memory, a decrease in visual acuity, psychomotor ability, and visual learning was reported in workers (Kumar et al. 1993). It is possible, however, that during occupational exposure, such as electroplating operations, chemicals other than cyanide may have contributed to the effects observed.

The severity of neurological effects in humans after acute oral exposure to cyanide are dose-related. The symptoms vary from tremor and headache (Chen and Rose 1952; Lasch and El Shawa 1981) to deep coma

and death in central respiratory arrest (Lasch and El Shawa 198 1; Thomas and Brooks 1970). Pathological changes that may occur in the central nervous system during acute exposure to high doses may complicate recovery. Severe Parkinsonism was one of the effects noted in four case reports resulting from severe acute oral exposure to cyanide (Carella et al. 1988; Grandas et al. 1989; Rosenberg et al. 1989; Uitti et al. 1985). Chronic exposure to cyanogenic glycosides in certain cassava diets may lead to multiple neuropathies in exposed populations (Howlett et al. 1990; Ministry of Health, Mozambique 1984; Monekosso and Wilson 1966; Money 1958; Osuntokun 1968, 1972; Osuntokun et al. 1969; Tylleskar et al. 1994). Among those observed were hyperreflexia or spastic paraparesis of the extremities, spastic dysarthria, visual and hearing difficulties, and cerebellar signs. In addition, epidemics of Konzo, a neurological disease characterized by the sudden onset of varying degrees of symmetric, isolated, nonprogressive spastic paraparesis, have occurred in Africa and have been associated with high dietary cyanide exposure from "bitter" cassava that was not fully processed due to a shortening of the cassava processing time (Tylleskar et al. 1994). It should be mentioned, however, that a recent study reported the isolation of scopoletin, a potent hypotensive and spasmolytic agent, from cassava roots (Obidoa and Obasi 1991) and it is possible that this substance, which remains in cassava during processing (rather than cyanide), is the etiological agent in the tropical ataxic neuropathy observed among cassava eaters (Obidoa and Obasi 1991).

Depending on the dose of cyanide given to animals, neurological effects of varying severity occurred. Tremors, convulsions, and lethargy were seen in rats treated with potassium silver cyanide for 90 days (Gerhart 1987b). Depressed activity was the only neurological sign found in rats exposed to lower doses of total cyanide given as copper cyanide for the same period (Gerhart 1987a). Myelin degeneration of spinal cord tracts was found in rats treated with potassium cyanide for 11.5 months (Philbrick et al. 1979). Similar to inhalation exposure effects, behavioral changes were found in pigs following intermediateduration oral exposure to cyanide as potassium cyanide; however, the animals were experimentally compromised as they were starved (Jackson 1988). In many studies, however, neurological effects occurred at high cyanide exposure levels. Extensive degenerative changes have been produced experimentally in the brain by cyanide treatment (Haymaker et al. 1952; Hirano et al. 1967; Levine 1969; Levine and Stypulkowski 1959a).

Convulsions and coma were also reported in humans (Dodds and McKnight 1985; Trapp 1970) and in animals (Fairley et al. 1934; Walton and Witherspoon 1926) following acute dermal exposure to cyanide.

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The nervous system is the most sensitive target for cyanide toxicity, partly because of its high metabolic demands. High doses of cyanide can result in death via central nervous system effects, which can cause respiratory arrest. In humans, chronic low-level cyanide exposure through cassava consumption (and possibly through tobacco smoke inhalation) has been associated with tropical neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy. It has been suggested that defects in the metabolic conversion of cyanide to thiocyanate, as well as nutritional deficiencies of protein and vitamin B_{50} and other vitamins and minerals may play a role in the development of these disorders (Wilson 1965).

Rats treated with a single dose of sodium cyanide subcutaneously developed necrotic lesions of the corpus callosum and optic nerve (Lessell 1971). High mortality was observed among exposed animals. Additional inhalation and oral studies in animals have shown that cyanide exposure leads to encephalopathy in both white and gray matter. In particular, damage has been observed in regions such as the deep cerebral white matter, the corpus callosum, hippocampus, corpora striata, pallium, and substantia nigra. White matter may be more sensitive because of its relatively low cytochrome c oxidase content. These effects have been observed following acute (Levine and Stypulkowski !959a, 1959b) and chronic exposures (Hertting et al. 1960). It appears that necrosis is the most prevalent effect following acute exposure to high concentrations of cyanide, whereas demyelination is observed in animals that survive repeated exposure protocols (Bass 1968; Ibrahim et al. 1963). The mechanism of demyelination is not completely understood, but the experimental evidence suggests that a direct effect of cyanide on white matter may not be necessary. It has been suggested that local edema affecting the olygodendrocytes and caused by vascular changes triggered by cyanide represent a primary event in demyelination (Bass 1968; Ibrahim et al. 1963). One characteristic of cyanide intoxication appears to be the inability of tissues to utilize oxygen. Consistent with this view is a report that in cyanide-intoxicated rats arterial pO_2 levels rose while carbon dioxide levels fell (Brierley et al. 1976). The authors suggested that the low levels of carbon dioxide may have led to vasoconstriction and reduction in brain blood flow; therefore brain damage may have been due to both histotoxic and anoxic effects. Partial remyelination after cessation of exposure has been reported, but it is apparent that this process, unlike the peripheral nervous system, is slow and incomplete (Hirano et al. 1968). The topographic selectivity of cyanide-induced encephalopathy may be related to the depth of acute intoxication and the distribution of the blood flow, which may result in selected regions of vascular insufficiency (Levine 1969).

Several recent studies have suggested that disruption of neuronal calcium regulation may be important in the manifestation of cyanide-induced neurotoxic events following acute exposure. Cyanide decreases the ATP/ADP ratio, or energy charge (Isom et al. 1975), and thus alters energy-dependent processes such as

cellular calcium homeostasis (Johnson et al. 1986). Elevated levels of intracellular calcium in a cyanide exposed, presynaptic squid neuron were observed in an in vitro study (Adams et al. 1985). Elevated levels of neuronal calcium may initiate release of neurotransmitters from the presynaptic terminal, which can activate the nervous system (Maduh et al. 1990a). Levels of whole-brain calcium increased when potassium cyanide was administered subcutaneously to mice (Johnson et al. 1986). These increases were correlated with cyanide-induced tremors (Johnson et al. 1986). Increases in intracellular calcium have also been associated with cyanide-induced effects on vascular smooth muscle and cardiac muscle, possibly inducing cell damage (Allen and Smith 1985; Robinson et al. 1985a). These effects may result from ischemia-induced increases in extracellular potassium, which in turn may enhance cellular permeabilities to calcium (Robinson et al. 1985b). Furthermore, changes in cytosolic pH and a dysfunction of hydrogen ion handling mechanisms were observed in neuronal cells exposed *in vitro* to cyanide (Maduh et al. 1990b).

In rat neonatal cerebellar granule cells in culture, cyanide increases both reactive oxygen species (RS) and nitric oxide (NO) (Gunasekar et al. 1996). Blockade of glutamate receptors with MK801 markedly reduced both ROS and NO and significantly protected the cells from cyanide damage. Thus, cyanide releases glutamate (Pate1 et al. 1993) which activates NMDA type glutamate receptors which in turn results in increased levels of ROS and NO. It was suggested that NO and ROS react to form a cytotoxic peroxynitrite anion which mediates neurotoxic effects of cyanide.

Recent studies have shown that cyanide releases catecholamines from rat pheochromocytoma cells and brain slices (Kanthasamy et al. 1991b), from isolated bovine adrenal glands (Borowitz et al. 1988), and from the adrenals of mice following subcutaneous injection of high doses of potassium cyanide (Kanthasamy et al. 1991b). Thus, it was proposed that the cardiac and peripheral autonomic responses to cyanide are partially mediated by an elevation of plasma catecholamines (Kanthasamy et al. 1991b).

Reproductive Effects. No studies were located regarding reproductive effects in humans after any route of exposure. Increased resorptions following oral exposure of rats to cyanogenic glycosides in a cassava diet (Singh 1981) and increased gonadal weight in male rats exposed to copper cyanide (Gerhart 1987a) or potassium silver cyanide (Gerhart 1987b) for 90 days were noted. A reduction in the spermatogenic cycle, testicular germ cell sloughing and degeneration, and occasional abnormal cells were noted in dogs fed rice with sodium cyanide added and in dogs fed a cassava diet (Kamalu 1993). A number of reproductive effects were observed following exposure of rats and mice to sodium cyanide in the drinking water for 13 weeks (NTP 1993). In male rats, decreases in the left caudal epididymal weight

left epididymis weight, left testis weight, spermatid heads, and spermatid counts were noted. In female rats, significantly more time was spent in proestrus and diestrus stages, and less time was spent in estrus and metes&us stages, while in male mice, a significant decrease in the left epididymal and caudal epididymal weights was noted, but no changes in sperm motility or spermatid head density were observed. This study was used as the basis for the oral intermediate MRL. In contrast, no reproductive effects were reported in hamsters exposed to cassava during gestation (Frakes et al. 1986a). Thus, it is possible that exposure to cyanide could lead to reproductive effects in humans.

Developmental Effects. No studies were located regarding developmental effects in humans after any route of exposure and in animals after inhalation and dermal exposure. However, studies in rats (Singh 1981) and hamsters (Frakes et al. 1986a) fed a cassava diet suggested that cyanide may have teratogenic and fetotoxic effects at maternally toxic doses, but Singh (1981) indicated that the results should be interpreted with caution due to the preliminary nature of the report and also indicated that the effects could have been due to the low protein content of the cassava diet. In contrast, Frakes et al. (1986a) clearly showed that the cyanogenic glycosides in the cassava diet or intubation of the principal cyanogenic glycoside (linamarin) (Frakes et al. 1985) were responsible for the adverse developmental effects, since a group of animals fed a diet that resembled cassava in nutritional value, but lacked the cyanogenic glycosides, had only reduced body weight and did not exhibit increased runting or decreased ossification. Similarly, in hamsters, oral doses of D,L-amygdalin also produced teratogenic effects (Willhite 1982), but only at doses that also produced maternal signs of systemic cyanide poisoning. Furthermore, subcutaneous infusions of sodium cyanide to pregnant hamsters increased the incidences of neural tube defects in the offspring (Doherty et al. 1982). In contrast, no teratogenic effects were reported in rats (Tewe and Maner 1981a) or in pigs (Tewe and Maner 1981b) exposed to cassava alone or supplemented with potassium cyanide. Decreased growth was noted in weanling rats of cyanide exposed dams in a two-generation exposure study (Tewe and Maner 1981a). In contrast to oral exposure, no teratogenic effects were observed in hamsters that received d, 1 -amygdalin intravenously (Willhite 1982). The teratogenic effects observed after oral amygdalin and linamarin exposure were due to cyanide releasec by bacterial beta glucosidase in the gastrointestinal tract (Frakes et al. 1985, 1986b; Willhite 1982). The possibility that chronic cyanide consumption, as in cyanogenic plant foods, could cause developmental effects in humans cannot be ruled out.

Genotoxic Effects. *In vitro* genotoxicity studies are summarized in Table 2-4. Cyanide in the form of potassium cyanide tested negative in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, TAlOO (De Flora 1981), TA97, and TA102 (De Flora et al. 1984). A positive mutagenic response was

Table 2-4. Genotoxicity of Cyanide *In Vitro*

Species (test system)	End point	Results		Reference	Form
		With activation	Without activation		
Prokaryotic organisms:					
Salmonella typhimurium TA82, TA102	Reverse mutation	–	Not tested	De Flora et al. 1984	KCN
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	De Flora 1981	KCN
S. typhimurium	Reverse mutation			Kushi et al. 1983	HCN
TA98		–	–		
TA100		(+)	+		
Escherichia coli WP67, CM871, WP2	DNA repair test	–	–	De Flora et al. 1984	KCN
S. tymphimurium TA97, TA98, TA 100, TA 1535	Reverse mutation	–	–	NTP 1993	NaCN
Eukaryotic organisms: HeLa cells	DNA synthesis inhibition	–	–	Painter and Howard 1982	KCN

DNA = deoxyribonucleic acid; HCN = hydrogen cyanide; KCN = potassium cyanide; NaCN = Sodium cyanide; – = negative result; + = positive result; (+) = weakly positive result

reported for hydrogen cyanide in strain TA100without metabolic activation (Kushi et al. 1983). Adding S-9 mix to the culture decreased the induction of reverse mutations by cyanide to 40% of the nonactivated reaction. Negative results were also obtained in the DNA repair test in *Escherichia coli* WP67, CM871, and WP2 with potassium cyanide (De Flora et al. 1984). Cyanide in the form of sodium cyanide tested negative in *S. typhimurium* strains TA97, TA98, TA100, and TA 1.535, with and without metabolic activation (NTP 1993).

Only one *in viva* study was located. No testicular DNA-synthesis inhibition was detected in mice after a single oral dose of 1 mg/kg cyanide as potassium cyanide (Friedman and Staub 1976). The results indicate that cyanide, especially in a form of salts, is not mutagenic.

Cancer. No studies were located regarding carcinogenic effects of cyanide exposure in humans or animals following any route of exposure. Therefore, no hypothesis can be made as to whether or not an increased risk of cancer can be expected in populations exposed to cyanide.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAXNRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to cyanide are discussed in Section 2.6.1.

2. HEALTH EFFECTS

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by cyanide are discussed in Section 2.6.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic, or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.8, Populations That Are Unusually Susceptible.

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Cyanide

Methods are available to measure levels of cyanide and its metabolite, thiocyanate, in blood and urine. High blood cyanide levels of 250-300 μg/l00 mL were reported in cases of death from cyanide poisoning (Vogel et al. 198 1). The relationship between increased exposure and increased urine levels of thiocyanate was demonstrated in workers exposed occupationally to 6.4-10.3 ppm cyanide in air (El Ghawabi et al. 1975). In another study, blood cyanide concentrations varied from 0.54 to 28.36 μg/l00 mL in workers exposed to ≈ 0.2-0.8 ppm cyanide in air and from 0.0 to 14.0 μg/l00 mL in control workers (Chandra et al. 1988). Correspondingly, blood thiocyanate concentrations were 0.05-2.80 mg/100 mL in exposed workers and 0.02-0.88 mg/100 mL in control workers, respectively. Data obtained from the controls indicate that cyanide can be detected in populations exposed to low cyanide levels in the environment. Cyanide-containing food, metabolism of certain drugs, and combustion of nitrogenous polymers are among several sources of cyanide exposure. Furthermore, industrially polluted air, soil, and water may contribute to higher environmental cyanide levels.

Several studies showed increased cyanide and thiocyanate levels in body fluids of smokers. The difference between smokers and nonsmokers can be quite distinct (Maliszewski and Bass 1955). Mean thiocyanate levels in smokers and nonsmokers, respectively, were found to be 7.1 and 2.0 μg/mL in plasma, 75.7 and 20.3 μg/mL in saliva, and 12.3 and 2.1 μg/mL in urine. A more recent study also

reported on mean thiocyanate levels in smokers and nonsmokers, respectively (Jarvis 1989). Levels reported were 7.1 and 2.9 μg/mL in plasma, 142 and 76 μg/mL in saliva, and 9.0 and 5.8 μg/mL in urine. Another study found a correlation between the number of cigarettes smoked per day and the thiocyanate levels in plasma and in saliva (Yamanaka et al. 1991). Based on changes in salivary thiocyanate in 6 smokers who stopped smoking, this study estimated the half-life of salivary thiocyanate to be 9.5 days. In addition, infants living in homes with family members who smoked heavily were found to have significantly higher serum thiocyanate levels than those infants who were not exposed to cigarette smoke in the home (Chen et al. 1990). It is unclear whether passive smoking (exposure of a nonsmoker to air contaminated with tobacco smoke) is a factor in elevated fetal serum thiocyanate levels. In one study, fetal thiocyanate levels were increased in association with passive smoking in the home (Bottoms et al. 1982), while another study did not report an association (Hauth et al. 1984).

Whether it is more appropriate to use whole blood or plasma for measuring cyanide concentrations has been the subject of several reports. Cyanide plasma levels are usually about one-third to one-half, depending on the species, those found in whole blood (Ballantyne 1983a). However, they can more closely reflect the actual tissue dose. Furthermore, cyanide was found to attach more readily to plasma albumin than to hemoglobin (McMillan and Svoboda 1982). It was suggested that hemoglobin in erythrocytes binds cyanide molecules, but does not play any role in their metabolism. Some authors argue cyanide in red blood cells may be biologically active (Way 1984). In addition, it is known that cyanide rapidly leaves serum and plasma, especially in the first 20 minutes. It may be appropriate to measure cyanide in both whole blood and plasma. Whole blood samples can be stored at 4 °C for several weeks with little change in cyanide content.

In cyanide-poisoning cases, any blood levels of cyanide >0.2 μ/L indicate a toxic situation (Berlin 1977). However, because cyanide binds tightly to cytochrome c oxidase, serious effects can also occur at lower levels; therefore, the clinical condition of the patient should be considered when determining proper therapy.

An almond-like smell in the breath of a poisoned patient can warn a physician that the individual may be suffering from cyanide poisoning. Approximately 60-70% of the population can detect the bitter almond odor of hydrogen cyanide. The odor threshold for those sensitive to the odor is estimated to be l-5 ppm in the air. However, even at high toxic concentrations up to 20% of all individuals are genetically unable to smell hydrogen cyanide (Snodgrass 1996). Some effects of cyanide that can also be used to monitor exposure are discussed in Section 2.5.2.

2.6.2 Biomarkers Used to Characterize Effects Caused by Cyanide

Cyanide can inhibit enzymatic activity by binding to some metallic moieties in metalloenzymes (Ardelt et al. 1989; Way 1984) and cytochrome c oxidase is especially sensitive to cyanide inhibition. Consequent to the inhibition, theoretically, oxygen cannot be used and histotoxic anoxia occurs. Death is caused by respiratory failure. Dyspnea, palpitations, hypotension, convulsions, and vomiting are among the first effects of acute cyanide poisoning (see Section 2.2). Ingestion of amounts 2 50-100 mg sodium or potassium cyanide may be followed by almost instantaneous collapse and cessation of respiration (Hartung 1982). Data summarized by Hartung (1982) indicate that exposure to a concentration in air of 270 ppm causes immediate death; concentrations of 181 ppm and 135 ppm are fatal after 10 and 20 minutes of exposure, respectively; concentrations between 45 and 55 ppm can be tolerated for 30-60 minutes with immediate or late effects; and 18-36 ppm may produce slight symptoms after several hours of exposure. Following chronic exposure, cyanide has been associated with the development of tropical neuropathy, tobacco amblyopia, and Leber's hereditary optic atrophy (Wilson 1965). Chronic exposure to cyanide arising from consumption of cyanogenic plant foods has also been connected with the occurrence of endemic goiter (Delange and Ermans 1971).

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.7 INTERACTIONS WITH OTHER CHEMICALS

A number of compounds act in synergy with cyanide to produce toxic effects. In smoke, hydrogen cyanide may interact with other toxicants (Birky and Clarke 198 1). High blood cyanide levels were found in fire victims; however, the carboxyhemoglobin levels were also high. Thus, it is difficult to assess the significance of hydrogen cyanide in the toxicity. The authors suggested that sublethal concentrations of hydrogen cyanide may interact with other toxicants to potentiate the toxic and lethal effects. They also speculated that cyanide could increase incapacitation of the victim, preventing escape, so that the victim could be exposed to high levels of carbon monoxide.

In an investigation to examine toxicological interactions of the primary fire gases, the additive, synergistic, or antagonistic effects of combinations of hydrogen cyanide with carbon monoxide or with carbon dioxide on the 30-minute LC_{50} value for hydrogen cyanide alone were determined in rats (Levin et

al. 1987). Co-exposure of rats to hydrogen cyanide (LC_{50} = 110 ppm) and carbon monoxide (LC_{50} = 4,600 ppm) resulted in lethal effects of these two gases that were additive. In contrast, co-exposure to hydrogen cyanide and 5% carbon dioxide (not lethal by itself) resulted in an increase in lethality of hydrogen cyanide, reflected as a decrease of the hydrogen cyanide LC_{50} value to 75 ppm. Dodds et al. (1992) also investigated the interaction between cyanide and carbon monoxide in rats, and found an additive effect on certain parameters, including lactate elevation and neurologic index.

Addition of sodium cyanide (5 mmol) and tributyltin (10 μmol) to human erythrocyte suspensions resulted in a synergistic increase in tributyltin-induced hemolysis (Gray et al. 1986). Mechanisms are not clear, but may involve elevated pH of high sodium cyanide concentrations.

Synergism has also been observed between cyanide and ascorbic acid. Guinea pigs exhibited increased toxic effects when treated with ascorbic acid prior to oral administration of potassium cyanide (Basu 1983). When guinea pigs were treated solely with potassium cyanide, 38% exhibited slight tremors, whereas 100% of those treated with ascorbic acid and potassium cyanide exhibited severe tremors, ataxia, muscle twitches, paralysis, and convulsions. It has been suggested that this synergistic effect results from the ability of ascorbic acid to compete with cyanide for cysteine, thus diminishing the detoxication of cyanide.

Antidotes for cyanide poisoning have been intensively studied and reviewed (Way 1984). Cyanide antagonists can be classified into two general groups: those that act as sulfane sulfur donors for rhodanese catalyzed cyanide detoxification and those that induce chemical binding of cyanide. Sulfur donors include sodium thiosulfate, polythionates, and thiosulfates. Sodium thiosulfate has been successfully used as an antidote against cyanide poisoning in humans for decades (Way 1984). A pharmacokinetic study in dogs demonstrated that intravenous administration of thiosulfate increased the detoxification rate of intravenously given cyanide to thiocyanate over 30 times (Sylvester et al. 1983). Pretreatment with thiosulfate decreased the biological half-life of cyanide from ≈ 39 minutes to ≈ 15 minutes and also decreased the volume of distribution of cyanide from 498 mL/kg to 204 mL/kg. Thiosulfate pretreatment had prophylactic effects in guinea pigs exposed to cyanide by intravenous infusion (Mengel et al. 1989). The protection lasted for several hours depending on the dose of thiosulfate administered.

Antagonists that induce the chemical binding of cyanide to sites other than cytochrome c oxidase include sodium nitrite, amyl nitrite, and hydroxylamine. These compounds generate methemoglobin, which competes with cytochrome c oxidase for cyanide to form cyanmethemoglobin (Way 1984). Sodium nitrite

has been effectively used in the therapy of cyanide intoxication in humans especially in combination with sodium thiosulfate (Smith 1996; Way 1984). Studies in mice demonstrated that intraperitoneal pretreatment with sodium nitrite more than doubled the LD_{50} value of intraperitoneally administered sodium cyanide from 3.18 to 7.95 mg CN^-/kg (Kruszyna et al. 1982). Peak methemoglobinemia was 35% at 40 minutes. Other methemoglobin generating agents seemed to be less effective. 4-Dimethylaminopropiophenol enhanced the LD_{50} value to 6.36 mg CN^-/kg and hydroxylamine to 4.66 mg CN^-/kg with peak methemoglobinemia being 40% and 36%, respectively at 7 minutes. The data suggested that sodium nitrite, a slow methemoglobin former, gave prolonged protection against cyanide, while animals treated with fast methemoglobin formers died later on, probably due to the cyanide release from the cyanmethemoglobin pool. An improvement of cyanide-altered cerebral blood flow was observed in dogs treated with sodium nitrite or 4-dimethylaminophenol following intravenous injection of hydrogen cyanide (Klimmek et al. 1983).

Cobalt-containing compounds may also function as binders by forming a stable complex with cyanide. A dramatic antagonism of the lethal effects of potassium cyanide was reported when cobaltous chloride was administered to mice along with sodium thiosulfate (Isom and Way 1974a). The authors suggested that this synergistic antidotal effect of cobaltous chloride may be associated with the physiological disposition of the cobaltous ion and its ability to chelate both thiocyanate and cyanide ions. This ability is also utilized when (dicobalt ethylenediamine tetra-acetate acid (CO_2EDTA) is used as a cyanide antidote. An improvement of cerebral aerobic metabolism and blood flow was observed in dogs treated with 10 mg/kg Co_2EDTA intravenously following intravenous application of 1.6 mg CN^-/kg as potassium cyanide (Klimmek et al. 1983). A lower molecular weight porphyrin cobalt compound than hydroxocobalamin (CoTPPS) was used as an antidote to the lethal effects of cyanide (McGuinn et al. 1994). The interaction with hydroxocobalamin (see Section 2.3.3) was also proposed as a mechanism for cyanide detoxification in cases of acute poisoning. It was demonstrated that intravenous administration of hydroxocobalamin (50-250 mg/kg) prior to or after intraperitoneal injection of potassium cyanide prevented lethality and decreased cyanide-induced toxic effects in mice (Mushett et al. 1952).

Pretreatment of rats with chlorpromazine (10 mg/kg intramuscularly) and sodium thiosulfate (1,000 mg/kg intraperitoneally) greatly decreased or abolished the increase in plasma creatine kinase observed in rats exposed to hydrogen cyanide at 200 ppm for 12.5 minutes (O'Flaherty and Thomas 1982). In an in vitro study, chlorpromazine and 4,4'-diisothiocyano-2,2'-stilbene disulfonic acid reduced cyanide-induced contractions in vascular smooth muscle (Robinson et al. 1985a). It was suggested that chlorpromazine

prevents cyanide-induced calcium influx and reduces peroxidation of membrane lipids (Maduh et al. 1988).

The ability of cyanide to combine with carbonyl groups of some intermediary metabolites (e.g., sodium pyruvate, a-ketoglutarate) to form cyanohydrin has been used for antidotal purposes. Pretreatment of mice with 1 g/kg sodium pyruvate intraperitoneally prior to subcutaneous injection of potassium cyanide caused an increase in the LD_{50} values from 3.1 to 5 mg CN^-/kg (Schwartz et al. 1979). Sodium pyruvate also prevented the development of convulsions in cyanide-exposed mice. Similarly, intraperitoneal pretreatment of mice with 2 g/kg α-ketoglutarate before the intraperitoneal injection of potassium cyanide increased the LD_{50} value from 2.68 to 13.32 mg CN^-/kg (Moore et al. 1986). It was further demonstrated that both sodium pyruvate and a-ketoglutarate enhanced the antidotal effects of other cyanide antagonists (e.g., sodium thiosulfate, sodium nitrite) (Moore et al. 1986; Schwartz et al. 1979).

A striking protection against cyanide can be elicited by an new conceptual approach, employing carrier erythrocytes containing highly purified rhodanese. Several studies have shown that resealed erythrocytes containing rhodanese and sodium thiosulfate rapidly metabolize cyanide to the less toxic thiocyanate (Cannon et al. 1994; Petrikovic et al. 1995). Maduh and Baskin (1994) showed that rhodenase may be regulated by protein phosphorylation and treatments that alter the phosphorylation state of rhodenase may affect cyanide detoxification via formation of thiocyanate.

Several papers discuss the effects of oxygen alone or with other compounds on cyanide toxicity. Oxygen alone results in minimal antagonism in mice injected with potassium cyanide and only slightly enhances the antagonistic effects of sodium nitrite (Sheehy and Way 1968). The antidotal effect of sodium thiosulfate alone or in combination with sodium nitrite, was enhanced by oxygen.

Oxygen-treated mice did not show behavioral signs of cyanide intoxication below doses of 2.4 mg CN^-/kg as potassium cyanide; whereas air-treated animals showed effects such as gasping, irregular breathing, and convulsions at levels as low as 1.2 mg CN^-/kg as potassium cyanide (Isom et al. 1982). When mice were pretreated with sodium nitrite and sodium thiosulfate and either air or oxygen, the dose of potassium cyanide needed to cause a 59% inhibition of brain cytochrome c oxidase more than doubled in mice in an oxygen atmosphere; all points on the oxygen curve differed significantly from the air-treatment curve.

A striking enhancement of the oxidation of glucose to carbon dioxide was observed when oxygen, sodium nitrite, and sodium thiosulfate were given to mice dosed at 18 mg CN^-/kg as potassium cyanide; no

enhancement was noticed at 4 or 6 mg CN^-/kg as potassium cyanide (Isom and Way 1974b). These studies indicate that oxygen can be used in supporting classical cyanide antagonists in the therapy of cyanide poisoning, but even hyperbaric oxygen alone had no effect on cyanide poisoning in mice (Way et al. 1972). The mechanism of the action is not known, since cyanide inhibits the cellular utilization of oxygen through inhibiting cytochrome c oxidase and, theoretically, the administration of oxygen should have no effect or useful purpose (Smith 1996).

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to cyanide than will most persons exposed to the same level of cyanide in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of cyanide, or compromised function of target organs affected by cyanide. Populations who are at greater risk due to their unusually high exposure to cyanide are discussed in Section 5.6, Populations With Potentially High Exposure.

Persons with a metabolic disturbance in the conversion of cyanide to thiocyanate may be at greater risk. A defect in the rhodanese system and vitamin B_{12} deficiency have been associated with tobacco amblyopia and Leber's hereditary optic atrophy in persons exposed to cyanide in tobacco smoke (Wilson 1983).

A number of dietary deficiencies may increase the risk of deleterious cyanide effects. Iodine deficiency is involved in the etiology of such thyroid disorders as goiter and cretinism. These disorders may be exacerbated by excess exposure to cyanide (Delange and Ermans 1971; Ermans et al. 1972). Protein deficiencies and vitamin B_{12}, riboflavin and other vitamins and elemental deficiencies may subject people in the tropics who eat cassava to increased risks of tropical neuropathies (Makene and Wilson 1972; Osuntokun 1972; Osuntokun et al. 1969). However, a recent study reported that scopoletin, a potent hypotensive and spasmolytic agent found in cassava roots, may be the etiological agent in the tropical neuropathies observed among cassava eaters, rather than cyanide (Obidoa and Obasi 1991). Furthermore, children and women seem to be more susceptible to the endemic spastic paraparesis in the cassava-consumption regions (Rosling 1987). Studies that have uncovered more severe effects in nutritionally deprived animals (Kreutler et al. 1978; Rutkowski et al. 1985) provide support to the observations in humans.

2. HEALTH EFFECTS

In areas where cassava is a staple food, congenital hypothyroidism is present in 15% of newborns (Ermans et al. 1980), indicating that fetuses may be at a higher risk. Animal studies provide further evidence that fetuses may be at a higher risk than the general population. Developmental toxicity has been observed in rodents following inhalation, oral, and parenteral exposure to cyanide-containing compounds (Doherty et al. 1982, 1983; Frakes et al. 1985, 1986a; Singh 1981; Willhite 1982), but not free cyanide.

One group of people who may be at greater risk are those who are exposed to cyanide but are unable to smell the chemical (Kirk and Stenhouse 1953; Snodgrass 1996). Patients with motor neuron disease (amyotrophic lateral sclerosis) possess a disorder in cyanide detoxification that may result in their higher susceptibility to cyanide (Kato et al. 1985).

2.9 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to cyanide. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to cyanide. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to cyanide:

- Ellenhom, MJ and Barceloux, DG. 1988. *Medical Toxicology, Diagnosis and Treatment of Human Poisoning.* Elsevier Publishing. New York, New York;
- Gosselin RE, Smith RP and Hodge, HC. 1984. Clinical Toxicology of Commercial Products. 5th edition. 111-123-130. Williams and Wilkins, Baltimore, Maryland; and
- LaDou, JY. 1990. *Occupational Medicine.* Appleton & Lange. Norwalk, Connecticut and San Mateo, California.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to cyanide may occur by inhalation, ingestion, or by dermal contact, but the general population is more likely to be exposed by inhaling air or ingesting food or water contaminated with cyanide. General recommendations for reducing absorption of cyanide from inhalation and dermal exposure include removing the exposed individual from the contaminated area and removing the contaminated clothing (Ellenhorn and Barceloux 1988; Goldfrank et al. 1990; Stutz and Janusz 1988). If the eyes and skin are exposed, they should be flushed with water. However, in order not to become

secondary victims, rescuers may enter potentially contaminated areas only with self-contained breathing apparatus and protective clothing. Speed is essential during a rescue operation.

In order to reduce absorption of ingested cyanide, gastric lavage may be performed immediately after ingestion. Individuals exposed by any route are commonly administered 100% oxygen and assisted ventilation, including endotracheal intubation, as needed. Hyperbaric oxygen has been advocated when patients do no respond to standard therapy (Litovitz et al. 1983); however, studies in laboratory animals suggest hyperbaric oxygen is no more effective than normobaric oxygen (Way 1984). An antidotal combination of inhaled amyl nitrate and intravenous sodium nitrite and sodium thiosulfate are often indicated. Monitoring for metabolic acidosis, cardiac dysrhythmias, and possible pulmonary edema is suggested.

2.9.2 Reducing Body Burden

The primary target for cyanide toxicity is the central nervous system following both acute and chronic exposure. Exposure to high doses of cyanide can rapidly lead to death (see Section 2.2). Cyanide is not stored in the organism and one available study indicates that >50% of the received dose can be eliminated within 24 hours (Okoh 1983). However, because of the rapid toxic action of cyanide, development of methods that would enhance metabolism and elimination of cyanide is warranted.

Cyanide is metabolized in the body by two metabolic pathways that have been identified (Ansell and Lewis 1970). The first and major metabolic pathway involves the transfer of sulfane sulfurs from a donor to cyanide to yield thiocyanate (see Section 2.3). The reaction employs the enzyme rhodanese as a catalyst. Thiocyanate is a fairly stable compound and is excreted predominately in urine. Serum proteins (especially albumin) are a major internal pool of sulfane sulfurs. Their protective role against cyanide toxicity was confirmed in tests with laboratory animals (Rutkowski et al. 1985; Tewe and Maner 1980, 1982). Cyanide antagonists help convert cyanide to thiocyanate. Sodium thiosulfate is commonly used in cases of cyanide poisoning, (Bonsall 1984; Mengel et al. 1989; Schubert and Brill 1968; Sylvester et al. 1983). An increase in antidotal effect was noted when rhodanese was combined with thiosulfate (Frankenberg 1980). Similarly, other sulfane sulfur donors have protective effects against cyanide toxicity.

The second and minor metabolic pathway consists of the reaction of cyanide with cystine to yield cysteine and β-thiocyanoalanine (Wood and Cooley 1955). The latter is then converted to 2-imino-

4-thiazolidinecarboxylic acid and excreted in urine. Cystine has not been used for the purpose of mitigation of cyanide effects because its contribution to detoxification via this pathway is minor.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of acute cyanide toxicity is well understood (see Section 2.4). Cyanide inhibits the activity of some enzymes by binding to their metallic moiety. By blocking the action of cytochrome c oxidase, histotoxic hypoxia/anoxia develops rapidly in exposed organisms (Smith 1996). The ability of cyanide to bind to some metallic ions is utilized with antidotes that cause methemoglobinemia in exposed organisms. Cyanide binds to the ferric ion of methemoglobin to form inactive cyanmethemoglobin (see Section 2.6). Antidotes utilized for this purpose either clinically or experimentally include amyl nitrite, sodium nitrite, hydroxylamine, p-aminopropiophenone, 4-dimethylaminophenol, and primaquine (Bhattacharya 1995; Bright and Marrs 1987; Kruszyna et al. 1982; Scharf et al. 1992; Schubert and Brill 1968). The disadvantage of these antidotes is that the methemoglobinemia further aggravates the depletion of tissues from oxygen; therefore, antidote-induced methemoglobin levels need to be closely followed in clinical practice.

Cyanide's binding to metallic ions is also employed in a reaction with cobalt-containing compounds that yields cyanocobalamin (see Section 2.6). Cobalt compounds generally are not used because of their toxicity; however, Co,EDTA (Klimmek et al. 1983) and hydroxocobalamin (Benabid et al. 1987; Mengel et al. 1989; Mushett et al. 1952) have been used as antidotes both in clinical and laboratory trials. Cardiac toxicity from Co_2EDTA use under clinical conditions has raised caution in its clinical use, as the cardiac toxicity of cobalt is well known (Way 1984). Both of these antidotes have the advantage of not inducing methemoglobinemia. A recent study (McGuinn et al. 1994) used a lower molecular weight cobalt porphyrin compound (CoTPPS) as an antidote to the lethal effects of cyanide. This compound was found to have a high affinity for cyanide due to its low molecular weight, and it allows administration in threefold molar excess of binding sites over a lethal dose of cyanide. Similarly, cyanide forms stable complexes with selenite (Palmer and Olson 1979). It is possible that further research may develop other metal-containing compounds usable as cyanide antidotes.

In an effort to find additional antidotes that would not produce methemoglobinemia, compounds such as sodium pyruvate, dihydroxyacetone, α-ketoglutarate (Niknahad and O'Brien 1996), oxaloacetate, pyridoxal 5'-phosphate, chlorpromazine, and naloxone (Way 1984) have been introduced (see Section 2.7). Interactions of cyanide with carbonyl groups of these compounds lead to formation of inert cyanohydrin

intermediates (Keniston et al. 1987; Moore et al. 1986; Schwartz et al. 1979; Yamamoto 1989). Niknahad et al. (1994) demonstrated that dihydroxyacetone and glyceraldehyde are much more effective than pyruvate and a-ketoglutarate as cyanide antagonists, and Hume et al. (1995) showed that α-ketoglutaric acid and sodium thiosulfate are synergistic in their antidotal effects against hydrogen cyanide and sodium cyanide.

Pharmacological approaches to finding antidotes for cyanide are also under investigation. Maduh et al. (1995) examined the effects of a protein kinase C inhibitor, 1-5-(isoquinolinesulfonyl)-2 methylpiperazine (H-7), on cellular energy depletion caused by sodium cyanide. They reported that H-7 partially prevented cellular energy depletion and increased the number of surviving cells.

In addition, other chemicals such as a-adrenergic blocking agents like chlorpromazine (O'Flaherty and Thomas 1982; Way and Burrows 1976) or oxygen (Burrows et al. 1973; Sheehy and Way 1968) may be used to enhance the protective action of other antidotes. However, the mechanism of their action is not well understood. Further research for a potent and safe antidote, particularly among smoke inhalation victims who have carbon monoxide poisoning, to mitigate cyanide toxicity is desirable.

It must be stressed that the therapeutic value of the antidotes mentioned above is heavily dependent on the time lapse between intoxication and their use, since the usual course of inorganic cyanide poisoning is acute and proceeds at very high speeds.

Sun et al. (1995) reported that the nitric oxide generator, isosorbide dinitrate, is an effective cyanide antidote in mice. They showed that the mechanism does not involve methemoglobin formation and suggested that nitric oxide might antagonize the respiratory depressant effects of cyanide. Other more efficient nitric oxide generators may be very useful cyanide antidotes.

2.10 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cyanide is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of cyanide.

2. HEALTH EFFECTS

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

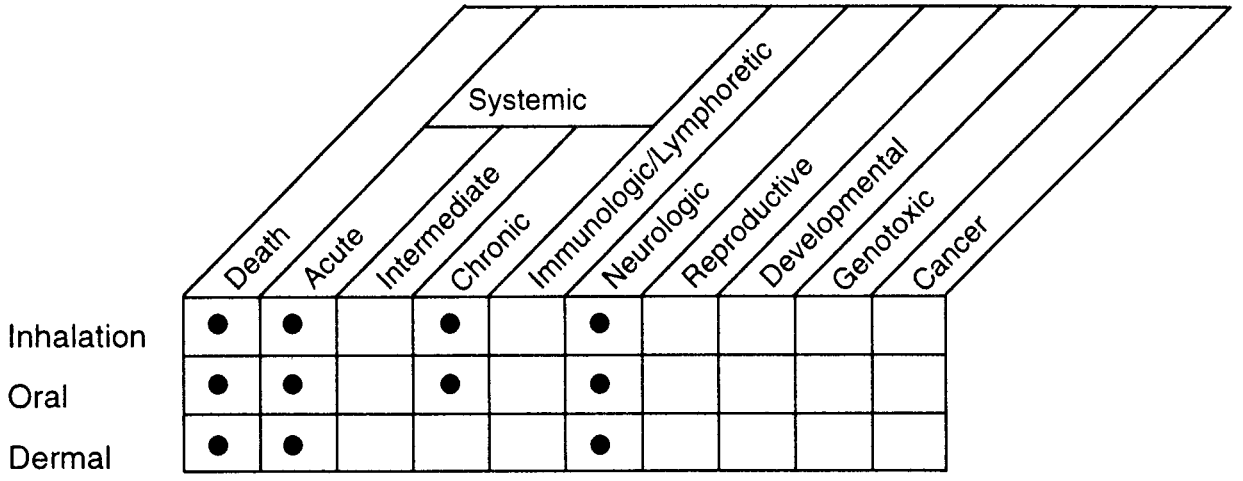
2.10.1 Existing Information on Health Effects of Cyanide

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cyanide are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of cyanide. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

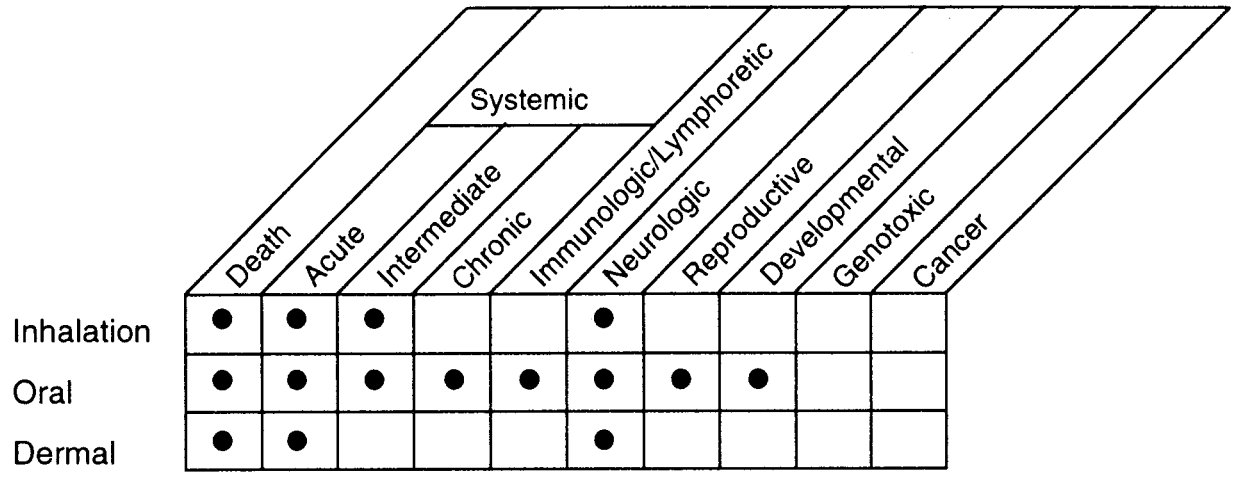
In the section that follows, data needs are identified for cyanide forms for which toxicity data were available and were, therefore, summarized in Section 2.2. These forms include primarily sodium cyanide, potassium cyanide, and hydrogen cyanide. As seen from Figure 2-6, information is available regarding death, systemic effects of acute exposure, and neurological effects in humans after inhalation, oral, and dermal exposure to cyanide. In addition, information is available regarding chronic systemic effects in humans after inhalation and oral exposure.

Data regarding death, systemic effects of acute exposure, and neurological effects were obtained for animals following inhalation, oral, and dermal exposure to cyanide. Furthermore, information was obtained regarding systemic effects after intermediate-duration inhalation and oral exposure, and chronic oral exposure. In addition, information exists regarding developmental and reproductive effects after oral exposure of animals to cyanide.

Figure 2-6. Existing Information on Health Effects of Cyanide



Human



Animal

● Existing Studies

2.10.2 Identification of Data Needs

Acute-Duration Exposure. The target organs of acute cyanide exposure are the central nervous system, respiratory system, and cardiovascular system. Exposure to high levels of cyanide leads rapidly to death. Lethality data are available in humans for acute inhalation (Dudley et al. 1942; Singh et al. 1989), oral (Gettler and Baine 1938), and dermal (Rieders 1971) exposures to hydrogen cyanide; however, specific exposure levels are often not available. Lethality studies were performed in several animal species, and LC_{50} and LD_{50} values were derived for inhalation (hydrogen cyanide and cyanogen) (Ballantyne 1983a), oral (potassium cyanide and sodium cyanide) (Ballantyne 1983a, 1988), and dermal (hydrogen cyanide, potassium cyanide, and sodium cyanide) (Ballantyne 1983a, 1988) exposures. The most common systemic effects observed were dyspnea and palpitations. The effects were seen in humans regardless of route of cyanide exposure. Since most of the animal studies reported lethality as an end point, information regarding acute systemic effects in animals is limited and no suitable NOAEL or LOAEL values are available to serve as the basis for MRLs. Additional acute studies by all routes using several dose levels and examining comprehensive end points would help to determine thresholds for known target organs and for any new target organs that might be identified. The information would be useful to populations living near hazardous waste sites that can be exposed to cyanide in contaminated water or soil for a short time.

Intermediate-Duration Exposure. No intermediate-duration studies were located regarding cyanide effects in humans. A few inhalation (Valade 1952) and oral (Gerhart 1987a, 1987b; Jackson 1988; Kamalu 1993; NTP 1993; Philbrick et al. 1979; Tewe and Maner 1981 b) studies in animals indicated that the target organs of intermediate-duration exposure to cyanide toxicity are the central nervous system (potassium cyanide and hydrogen cyanide) and the reproductive system (sodium cyanide). In addition, dermal, hematological, hepatic, and renal effects may be caused by oral exposure. No intermediateduration dermal studies were available. It is known, however, that cyanides can rapidly penetrate the skin and similar toxic effects are presumed. No intermediate-duration inhalation MRL could be derived because of the lack of data. An intermediate oral MRL of 0.05 mg/kg/day was derived from a study showing reproductive effects in rats exposed to 12.5 mg/kg/day cyanide in the drinking water for 13 weeks, as sodium cyanide (NTP 1993). This study is further described in the section on Reproductive Toxicity below. Additional intermediate-duration inhalation studies using several dose levels would be useful to determine threshold levels.

2. HEALTH EFFECTS

Chronic-Duration Exposure and Cancer. Some reports of occupationally exposed workers indicated that low concentrations of hydrogen cyanide may have caused neurological, respiratory, and cardiovascular effects (Blanc et al. 1985; Chandra et al. 1980, 1988; El Ghawabi et al. 1975; Kumar et al. 1992). The route of exposure was predominantly inhalation, although dermal exposure can also occur in the work place. The studies, however, lacked either information about exposure levels or used small cohorts of workers. Studies in populations that used cassava roots as a main source of their diet described the neurological effects of cyanide consumption (Osuntokun 1972, 1980). However, these effects may be due to a recently identified substance, scopeletin, rather than due to cyanide (Obidoa and Obasi 1991). For chronic exposure in animals, only one oral study in rats (hydrogen cyanide) was located (Howard and Hanzal 1955). However, the reliability of this study is low because of the unstable cyanide levels in their feed throughout the experiment due to evaporation of cyanide. Furthermore, no effects were found in the study besides nondose-related changes in weight gain in female rats, but not in male rats. No chronic studies in animals were located for the inhalation and dermal routes. Therefore, data are not sufficient to derive MRL values for chronic exposure. Additional chronic-duration studies in animals would be helpful to determine thresholds for target organs.

No studies were located regarding carcinogenicity of cyanide in humans or animals. The results of the chronic bioassays suggested above may contribute some new insights.

Genotoxicity. No human data are available on the genotoxicity of cyanide. In *vitro* studies with cyanide in the form of potassium cyanide did not show any mutagenic activity in *S. typhimurium* or *E. coli* (De Flora 1981; De Flora et al. 1984), and cyanide in the form of sodium cyanide tested negative in *SulmoneZla* strains TA97, TA98, TA100, and TA1535, with and without metabolic activation (NTP 1993). One study in *S. typhimurium* suggested that hydrogen cyanide may be mutagenic (Kushi et al. 1983); an increase in the induction of reverse mutations was noted without metabolic activation. No genotoxicity was found in one *in vivo* study with potassium cyanide in mice (Friedman and Staub 1976). In summary, no human studies are available and *in vitro* studies have shown primarily negative results. There are no structural reasons to suggest that cyanide may be genotoxic. Thus, it does not appear that further genotoxicity studies are needed at this time.

Reproductive Toxicity. No data were located regarding reproductive effects of cyanide in humans. One animal study reported increased resorptions in rats following oral exposure to a cassava diet (Singh 1981). Because some human populations use cassava roots as the main source of their diet, further information regarding this observation would be useful for these populations, but this is probably not a

concern for people living in the United States. Increased gonadal weight was found in male rats in 90-day oral studies of copper cyanide and potassium silver cyanide (Gerhart 1987a, 1987b). A number of reproductive effects, including decreases in left cauda epididymal weight, left testis weight, spermatid heads, and spermatid counts were noted in rats exposed to sodium cyanide in the drinking water for 13 weeks (NTP 1993). This study was used as the basis for the intermediate oral MRL. Thus, it appears that only limited value would be associated with further reproductive studies at this time.

Developmental Toxicity. No studies were located regarding developmental effects in humans exposed to cyanide by any route. Developmental studies in animals were performed only following oral exposure and contradicting results were obtained. Teratogenic effects of cyanide exposure were observed in rats and hamsters fed a cassava diet (Frakes et al. 1986a; Singh 1981), while no effects were found in rats and pigs fed cassava diets alone or supplemented with potassium cyanide in other studies (Tewe and Maner 1981 a, 1981b). Furthermore, growth retardation was the only effect in weanling rats in the second generation of a two-generation oral exposure study with potassium cyanide. More data regarding developmental toxicity in experimental animals would be useful to identify the possible risk for humans.

Immunotoxicity. No data were located regarding immunological effects in humans or animals after inhalation, oral, or dermal exposure to cyanide. A battery of immune function tests has not been performed in humans or animals but would be useful to clarify whether cyanide is an immunotoxin.

Neurotoxicity. The central nervous system is an important target for cyanide toxicity in humans and animals following exposure by all three routes. Acute inhalation exposure to high levels of cyanide, regardless of the form, leads quickly to death that is preceded by dyspnea, convulsions, and central nervous system depression (Bonsall 1984; Chen and Rose 1952; Peden et al. 1986; Potter 1950; Singh et al. 1989). Neurological and behavioral effects were observed in humans after chronic inhalation exposure to hydrogen cyanide in the workplace (Blanc et al. 1985; Chandra et al. 1988; El Ghawabi et al. 1975). Oral exposure to cyanide led to the development of severe peripheral neuropathies, and hearing and visual problems in those who used cassava as a staple in the diet (Osuntokun 1980). However, these effects may be due to a recently identified substance, scopeletin, rather than due to cyanide (Obidoa and Obasi 1991). Experimental studies in animals exposed to hydrogen cyanide or cyanide compounds by the inhalation (Purser et al. 1984; Valade 1952), oral (Philbrick et al. 1979), or dermal routes (Ballantyne 1983b), have found neurological effects similar to those seen in humans. Behavioral changes were reported in pigs after oral exposure to cyanide; however, the animals were experimentally compromised as they were starved (Jackson 1988). Additional studies for neurological effects for all routes and durations would be useful

for determining the NOAEL values for this most sensitive end point. Of particular value would be studies that correlate morphological changes, such as demyelination, with changes in higher functions, such as learning and memory.

Epidemiological and Human Dosimetry Studies. Human exposure to low levels of cyanide is quite common. Cigarette and fire smoke contain cyanide (Fiksel et al. 1981); it is used as a postharvest fumigant (Jenks 1979) and can even be detected in drinking water supplies (Fiksel et al. 1981). Furthermore, workers are exposed to cyanide in several industries (Blanc et al. 1985). Although several studies reported neurological and thyroid effects in workers chronically exposed occupationally, dose relationships of these effects are not known, and the effects may have been confounded by simultaneous exposure to other chemicals. Similarly, exact correlations between environmental exposures and cyanide levels in blood or urine were not established. Therefore, occupational and environmental studies that would provide data on exposure levels and concentrations found in body fluids would be useful. These studies might be useful for establishing cause/effect relationships that might lead to future monitoring of populations exposed to low levels of cyanide from dietary sources or contaminated waste sites. Furthermore, studies regarding the health status, including urinary thiocyanate as a biomarker, of such populations would be informative. Studies examining exposure to cyanide via cassava consumption would not be useful, since cassava is not normally consumed in the United States; additionally researchers have recently noted that another substance rather than cyanide may be the neurotoxic agent in cassava (Obidoa and Obasi 1991).

Biomarkers of Exposure and Effect.

Exposure. Concentrations, of cyanide and its metabolite thiocyanate can be measured in the blood, urine, and tissues. Since certain amounts of cyanide can always be found in the human tissues, urine, and expired air, only exposure to high doses can be detected by this way. Cyanide is metabolized in the body to thiocyanate in a reaction that is catalyzed by an enzyme rhodanese and mercaptopyruvate sulfur transferase (Ansell and Lewis 1970).

Effect. No biomarkers were identified that are useful for characterizing effects induced by exposure to cyanide. The target organs of cyanide toxicity are the central nervous system and the cardiovascular system. However, exposure to other chemicals may have similar effects. More studies to identify subtle biochemical changes to serve as biomarkers of effects of cyanide exposure would be useful.

2. HEALTH EFFECTS

Absorption, Distribution, Metabolism, and Excretion. Hydrogen cyanide, sodium cyanide, and potassium cyanide are readily absorbed following inhalation, oral, and dermal exposures (Ballantyne 1983a). Inhalation exposure provides the most rapid route of entry. Cyanide is distributed throughout the body and detoxified by a mitochondrial enzyme, rhodanese (Ansell and Lewis 1970). Other detoxification pathways include spontaneous reaction with cystine and the reaction with hydroxocobalamin. The severity and rapidity of the onset of effects depend on the route, dose, duration of exposure, and the cyanide compound administered. Once cyanides have been absorbed, excretion is similar in humans and animals. Cyanide metabolites are excreted primarily in urine, and small amounts of hydrogen cyanide are eliminated through the lungs (Farooqui and Ahmed 1982; Okoh 1983). Additional quantitative data on the toxicokinetics of cyanide would be useful, because there are few studies available that quantitate absorption and distribution. No data were found that dealt with saturation kinetics in cyanide metabolism, since cyanide is fatal long before saturation is reached.

Comparative Toxicokinetics. Several studies on cyanide lethality and toxicity indicate that the central nervous system, the reproductive system, and the thyroid gland are target organs in both humans and animals. Toxicokinetic studies have not been performed in humans; however, data regarding cyanide distribution have been obtained during autopsies in several lethal cases of poisoning following inhalation or oral exposure to hydrogen cyanide, sodium cyanide, or potassium cyanide (Finck 1969; Gettler and Baine 1938). Most of the toxicokinetic studies in animals were published between 1935 and 1965. As a result, much of the information is descriptive rather than quantitative, and the quantitative data presented were generated with inaccurate analytical equipment and methodologies. However, more recent studies in rats with hydrogen cyanide, sodium cyanide, and potassium cyanide indicate a pattern of distribution that is similar to that in humans (Ballantyne 1983a, 1983b; Yamamoto et al. 1982). Furthermore, a study regarding transocular exposure showed that tissue concentrations of cyanide in rabbits varied depending on the cyanide compound used (Ballantyne 1983a, 1983b). Detailed pharmacokinetic studies on cyanide and thiosulfate have been conducted in dogs (Sylvester et al. 1983). Additional toxicokinetic data in several species would be needed to identify the best model for assessing human risk.

Methods for Reducing Toxic Effects. The mechanism by which cyanide enters the blood stream in humans is not known; but due to the relatively small size of the molecule, it is possible that cyanide simply follows a concentration gradient. Some of the mechanisms of toxic action of cyanide are known: the compound inhibits the activity of various enzymes by binding to their metallic moiety. Cyanide antagonists, such as sodium thiosulfate, have been used as antidotes to cyanide poisoning by aiding in the conversion of cyanide to thiocyanate (Bonsall 1984; Mengel et al. 1989; Schubert and Brill 1968;

Sylvester et al. 1983). Other antidotes such as amyl nitrite, sodium nitrite, hydroxylamine, p-aminopropiophenone, 4-dimethylaminophenol, and primaquine work by binding to metallic ions and causing methemoglobinemia (Bright and Mans 1987; Kruszyna et al. 1982; Sharf et al. 1992; Schubert and Brill 1968). Additional research has been carried out on antidotes that would not produce methemoglobinemia (Klimmek et al. 1983; Niknahad and O'Brien 1996), and recent studies have examined the synergistic effects of several antidotes (Hume et al. 1995; Niknahad et al. 1994), as well as pharmacological approaches to finding antidotes for cyanide (Maduh et al. 1995).

2.10.3 Ongoing Studies

A number of ongoing studies concerning health effects and mechanisms of action associated with cyanide have been identified in the Federal Research in Progress (FEDRIP) database. A study at Purdue University is investigating the mechanisms of action of cyanide-induced neurotoxicity. A study at the University of Nevada is investigating the potential health effects from acute and intermediate exposure periods to sublethal levels of cyanide in drinking water. Symbiotech, Inc., is developing a pretreatment against hydrogen cyanide and cyanogen chloride when used as chemical warfare agents. Two additional ongoing studies were identified: the Department of Veterans Affairs is sponsoring a study testing the effect of two regimens of thiosulfate and nitroprusside on serum cyanide levels on post-operative patients receiving high levels of nitroprusside; a University of Alabama study is investigating the role of thiocyanate in human health (FEDRIP 1996).